A. M. A.
ARCHIVES OF
NEUROLOGY AND PSYCHIATRY

EDITORIAL BOARD

TRACY J. PUTNAM, Chief Editor
450 North Bedford Drive, Beverly Hills, California

HAROLD G. WOLFF, New York
STANLEY COBB, Boston
JOHN WHITEHORN, Baltimore
CHARLES D. ARING, Cincinnati
ROY R. GRINKER, Chicago
BERNARD J. ALPERS, Philadelphia
PERCIVAL BAILEY, Chicago
WILDER PENFIELD, Contributing Member, Montreal

RICHARD J. PLUNKETT, M.D., Chicago, Managing Editor

MAY 1952
VOLUME 67 NUMBER 5

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

TABLE OF CONTENTS FIRST PAGE

COLONIAL HALL
One of Fourteen units in "Cottage Plan"

For Nervous Disorders

Maintaining the highest standards for more than a half century, the Milwaukee Sanitarium stands for all that is best in the care and treatment of nervous disorders.

Photographs and particulars sent on request.

Josef A. Kindwall, M.D.
Carroll W. Osgood, M.D.
William T. Kradwell, M.D.
Benjamin A. Ruskin, M.D.
Lewis Danziger, M.D.
Russell C. Morrison, M.D.
H. V. Capparell, M.D.
LeRoy E. Bostian, M.D.

★

G. H. Schroeder, Business Manager

Chicago Office — 1117 Marshall Field Annex
Central 6-1162
Wednesday, 1 - 3 P. M.

MILWAUKEE SANITARIUM

WAUWATOSA • WISCONSIN

CONTENTS

Original Articles

Cell Rests in the Region of the Fourth Ventricle PAGE

Richard J. Brzustowicz, M.D., and James W. Kernohan, M.D., Rochester, Minn.

I. Their Site and Incidence According to Age and Sex 585

II. Histologic and Embryologic Consideration 592

III. Their Relationship to the Development of Gliomas 602

Studies on Anxiety Associated with Anticipation of Pain

Harris E. Hill, Ph.D.; Conan H. Kornetsky, M.S.; Harold G. Flanary, M.S., and Abraham Wikler, M.D., Lexington, Ky. 612

Combined Use of Ethyl Alcohol and Amobarbital (Amytal®) Sodium for Ambulatory Narcoanalysis

Michael M. Miller, M.D., Washington, D. C. 620

Incidence of Cavum Septi Pellucidi and Cavum Vergae in 1,032 Human Brains

Jess T. Schwidde, M.D., Iowa City 625

Occlusive Cerebrovascular Disease Simulating Brain Tumor

Gordon L. Smiley, M.D., Saginaw, Mich. 633

Subarachnoid Hemorrhage, Intracerebral Hemorrhage, and Intracranial Aneurysms

Anatole Dekaban, M.D., and Donald McEachern, M.D., Montreal, Canada 641

Rate of Advance of Hoffmann-Tinel Sign in Regenerating Nerves

S. Sunderland, M.D., D.Sc., and K. C. Bradley, M.B., F.R.A.C.S., Melbourne, Australia 650

Optic Atrophy Caused by an Arteriovenous Angioma

Lieutenant Raymond I. Band, Medical Corps, Army of the United States 655

Clinical and Electroencephalographic Effects of Prefrontal Lobotomy and Topectomy in Chronic Psychoses

Erich G. Krueger, M.D., and Henriette Loewenberg Wayne, M.D., Sc.D., New York .. 661

Reactions of Dogs Without Neocortex During Cycles of Addiction to Morphine and Methadone

Abraham Wikler, M.D., Lexington, Ky. 672

(Continued on Next Page)

Society Transactions

PAGE

Chicago Neurological Society 685

New York Neurological Society and New York Academy of Medicine, Section of Neurology and Psychiatry 686

Philadelphia Neurological Society 690

Philadelphia Neurological Society; New York Neurological Society, and New York Academy of Medicine, Section on Neurology and Psychiatry 692

Philadelphia Psychiatry Society 696

Regular Departments

Abstracts from Current Literature 702

News and Comment 721

Books 723

PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (three volumes): domestic, $15.00; Canadian, $16.50; foreign, $19.00. Single copies, 45 cents.

A. M. A. ARCHIVES OF INTERNAL MEDICINE—Monthly. Devoted to the publication of advanced original clinical and laboratory investigations in internal medicine. Illustrated. Annual subscription price (two volumes): domestic, $10.00; Canadian, $10.40; foreign, $11.00. Single copies, $1.00.

A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. Includes carefully prepared reviews, based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): domestic, $14.00; Canadian, $14.40; foreign, $15.50. Single copies, $1.25, except special numbers.

A. M. A. ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, annual reviews of special subjects, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original articles and general reviews in the field of pathology. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, $1.00, except special issues.

A. M. A. ARCHIVES OF INDUSTRIAL HYGIENE AND OCCUPATIONAL MEDICINE—Monthly. Devoted to the advancement of knowledge of the diseases of industry and to the publication of scientific investigation in this field. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00, including postage. Single copies, $1.00.

QUARTERLY CUMULATIVE INDEX MEDICUS—A complete subject and author index to the worth while current medical literature of the world. Issued twice a year. Volumes bound for permanent reference. Subscription price, calendar year: domestic, $20.00; Canadian, $22.00; foreign, $22.00.

SIX JOURNALS YOU NEED

For Increasing Your Professional Effectiveness

PEDIATRICS *The Journal of the American Academy of Pediatrics, edited by* **Hugh McCulloch.** Supplies advances in pediatrics that are applicable to daily work. Comprehensive coverage of all phases of child development and the treatment of children's diseases. Invaluable not only to the pediatrician but also to general practitioners, nutritionists, geneticists, psychologists, psychiatrists, sociologists, and other specialists. *Monthly. $12.00 a year in the U.S.A.*

JOURNAL OF NEUROPHYSIOLOGY *Edited by* **John F. Fulton.** For 14 years the principal avenue of publication for the continuously increasing stream of meritorious contributions in neurophysiology. The status of neurophysiology is presented so that a reader—even one not specializing in this field—may obtain a foundation for the understanding of developments. *Bi-monthly. $8.00 a year in the U.S.A.*

JOURNAL OF NEUROSURGERY *Journal of The Harvey Cushing Society. Edited by* **Louise Eisenhardt.** Read by leading neurosurgeons of the world. The steady growth of neurological surgery as a specialty is readily apparent in this beautifully produced journal which publishes articles relating primarily to neurosurgery, including studies in clinical neurophysiology, ophthalmology, radiology, and pathology. *Bi-monthly. $11.00 in the U.S.A.*

THE JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM *Published for the Endocrine Society. Edited by* **Willard O. Thompson.** A medium of publication preferred by foremost investigators and clinical authorities for the publication of their work in practical endocrinology. Valuable papers on goitre, diabetes, sterility and infertility, and gynecological endocrinology. Stresses current clinical and laboratory methods. *Monthly. $12.00 in the U.S.A.*

ENDOCRINOLOGY *(A Research Journal) Published for The Endocrine Society. Edited by* **E. W. Dempsey.** Well-informed investigators depend on this journal for a complete accounting of progress in endocrinology and associated fields. Ten to twelve original articles in each issue, presenting the results of fundamental endocrine research in the broadest interpretation. Specific information on new and standard endocrine products and materials. *Monthly. $12.00 a year in the U.S.A.*

THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE *Official Organ—The American Roentgen Ray Society and The American Radium Society. Edited by* **Lawrence Reynolds.** Comprehensive coverage of latest developments in these increasingly important fields. In each issue: 10 to 15 original articles by recognized authorities; specific information on new techniques and apparatus; abstracts of the world's radiological literature. *Monthly. $15.00 a year in the U.S.A.*

Each a leader in its field

CHARLES C THOMAS • PUBLISHER

Springfield • Illinois

INDEX TO

NEUROPSYCHIATRIC INSTITUTIONS SPECIAL SCHOOLS and SANITARIA

Advertising in

A.M.A. Archives of NEUROLOGY and PSYCHIATRY

Display announcements of the following institutions appear regularly in A. M. A. Archives of NEUROLOGY and PSYCHIATRY. For advertisements of those institutions which run on an every-other month basis it would be necessary to consult the advertising section of a previous or *subsequent issue.*

ADAMS HOUSE ..... Boston, Jamaica Plain, Mass.
James Martin Woodall, M.D., Medical Director

ANN ARBOR SCHOOL ..... 1700 Broadway, Ann Arbor, Mich.
Registrar

APPALACHIAN HALL ..... Asheville, N. C.
Wm. Ray Griffin, M.D.

BALDPATE, INC. ..... Georgetown, Mass.
G. M. Schlomer, M.D., Medical Director

BEVERLY FARM, INC. ..... Godfrey, Ill.
Dr. Groves B. Smith, Superintendent

BLYTHEWOOD ..... Greenwich, Conn.
George W. Henry, M.D., Medical Director

BROOKLEA FARM ..... Port Chester, N. Y.
George W. Henry, M.D.

CITY VIEW SANITARIUM ..... Nashville, Tenn.
Frank W. Stevens, M.D., Director

CLEARVIEW ..... Evansville, Ind.
Dr. Albert L. Crane, Medical Director

FAIRVIEW SANITARIUM ..... Chicago, Ill.
Dr. J. Dennis Freund, Medical Director

HARWORTH HOSPITAL ..... Detroit, Mich.
Mrs. J. Harrington, R.N., Superintendent

HIGHLAND HOSPITAL ..... Asheville, N. C.
B. Charman Carroll, Medical Director

INSTITUTE FOR SPEECH CORRECTION ..... Boston, Mass.
Samuel B. Robbins, Director

LIVERMORE SANITARIUM ..... Livermore, Calif.
O. B. Jensen, M.D., Superintendent and Med. Dir.

MIAMI MEDICAL CENTER ..... Miami, Fla.
P. L. Dodge, M.D.

MILWAUKEE SANITARIUM ..... Wauwatosa, Wis.

NORTH SHORE HEALTH RESORT ..... Winnetka, Ill.
Samuel Liebman, M.D., Medical Director

THE MARY POGUE SCHOOL ..... Wheaton, Ill.
U. S. Ayer, Manager

THE RING SANATORIUM ..... Arlington, Mass.
Benjamin Simon, M.D., Director

RIVER CREST SANITARIUM ..... Astoria, Queensboro, N. Y. City
and BELLE MEAD FARM COLONY ..... Belle Mead, N. J.
Dr. J. J. Kindred, Founder and Consultant

CARROL TURNER SANATORIUM ..... Memphis, Tenn.
Carrol C. Turner, M.D.

WESTBROOK SANATORIUM ..... Richmond, Va.
Rex Blankinship, M.D., Medical Director

THE CARROL TURNER SANATORIUM

Memphis, Tenn. • Route 10, Box 288

Located on the Raleigh-La Grange Road, five miles east of the city limits. Accessible to U. S. 70 (the Bristol Highway).

FOR THE DIAGNOSIS AND TREATMENT OF MENTAL AND NERVOUS DISORDERS

53½ acres of wooded land and rolling fields. Equipment new and modern, including the latest equipment for electro-shock, physical and hydrotherapy. Special emphasis is laid upon occupational and recreational therapy under the supervision of a trained therapist. An adequate nursing personnel gives individual attention to each patient.

THE LIVERMORE SANITARIUM

LIVERMORE, CALIFORNIA

San Francisco Office - 450 Sutter Street

For the Treatment of Nervous and Mental Diseases

THE HYDROPATHIC DEPARTMENT, for nervous and general patients; the Cottage Department, for mental patients. FEATURES: near Oakland and San Francisco; ideal climate; large beautiful grounds; hydrotherapy, athletic and occupational departments; clinical laboratory; large trained nursing force. Rates include these facilities: Room, suitable diet, and general nursing care. Booklet on request.

O. B. JENSEN, M.D., Superintendent and Medical Director — Consulting—J. W. Robertson, M.D.

THE MARY POGUE SCHOOL

Complete facilities for training retarded and epileptic children educationally and socially. Pupils per teacher strictly limited. Excellent educational, physical and occupational therapy programs.

Recreational facilities include riding, group games, selected movies under competent supervision.

Separate buildings for boys and girls under 24 hour supervision of skilled personnel.

Catalog on request.

G. H. Marquardt, M.D., *Medical Director* — Barclay J. MacGregor, *Registrar*

65 GENEVA ROAD,
WHEATON, ILLINOIS
(near Chicago)

Beautiful Miami Medical Center

A private hospital in a most picturesque setting. Facilities for treatment of acute medical and convalescent cases. Especially equipped for care of nervous and mental disorders, drug and alcoholic habits. Psychotherapy, Hydrotherapy, Diathermy. Insulin and Electric-Shock therapy.

MEMBER AMERICAN HOSPITAL ASSOCIATION

P. L. DODGE, M.D., *Medical Director and President*

MIAMI MEDICAL CENTER

1861 N. W. S. RIVER DRIVE
MIAMI, FLORIDA

"Beverly Farm"

INCORPORATED
Founded 1897
INCORPORATED 1922

11 buildings
220 acres of land
300 feet above
Mississippi River

HOME AND SCHOOL FOR
Nervous and Backward Children

Can accommodate 200 children, with contemplated educational improvements for a larger number. Can accept some suitable case for life.

Address all communications to **DR. GROVES B. SMITH, SUPERINTENDENT**
"Beverly Farm"
GODFREY, MADISON COUNTY, ILLINOIS

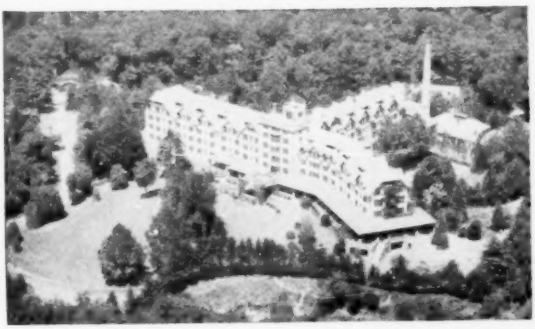
CITY VIEW SANITARIUM

For the diagnosis and treatment of mental and nervous disorders, alcoholism and drug addictions.

Established in 1907 by the late John W. Stevens, M.D. Fifty-two acres near city. Separate buildings for men and women. Two full-time psychiatrists. Electric shock and insulin therapy in selected cases. Psychotherapy. Occupational therapy. Adequate laboratory facilities.

NASHVILLE, TENNESSEE

Appalachian Hall



An institution for rest, convalescence, the diagnosis and treatment of nervous and mental disorders, alcohol and drug habituation.

Appalachian Hall is located in Asheville, North Carolina. Asheville justly claims an unexcelled all year round climate for health and comfort. All natural curative agents are used, such as physiotherapy, occupational therapy, shock therapy, outdoor sports, horseback riding, etc. Five beautiful golf courses are available to patients. Ample facilities for classification of patients. Room single or en suite with every comfort and convenience.

For rates and further information, write

APPALACHIAN HALL

Asheville, North Carolina

M. A. Griffin, M.D.
Wm. Ray Griffin, M.D.

CLEARVIEW

ON THE KRATZVILLE ROAD
EVANSVILLE, INDIANA

TELEPHONE 5-6181

A PRIVATE HOSPITAL FOR THE TREATMENT OF PATIENTS SUFFERING FROM NERVOUS AND MENTAL ILLNESS, ALCOHOLISM AND DRUG ADDICTION.

SEPARATE BUILDINGS FOR DISTURBED AND CONVALESCENT PATIENTS.

Equipped for Surgery

ELECTROENCEPHALOGRAPH
CLINICAL LABORATORY
ELECTROCARDIOGRAPH
STEREOSCOPIC X-RAY
BASAL METABOLISM
HYDROTHERAPY

Albert J. Crevello, M.D.
Diplomate, American Board of Psychiatry & Neurology, Inc.
MEDICAL DIRECTOR

BALDPATE, INC.

Georgetown, Mass.

Geo. 2131—Boston Office Be.-2-3911

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment; other methods such as *shock therapy, malaria* and *fever box* are used when indicated.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. Schlomer, M.D., *Medical Director*

FOR THE CARE AND TREATMENT OF

MENTAL AND NERVOUS DISORDERS

• ELECTRIC SHOCK • HYPERPYREXIA •

• INSULIN •

FAIRVIEW Sanitarium

2828 S. PRAIRIE AVE.
CHICAGO
Phone Calumet 4588

Newest Treatment for
ALCOHOLIC and NARCOTIC PATIENTS

Registered with the American Medical Association

J. DENNIS FREUND, M. D.
Medical Director and Superintendent

SPEECH DEFECTS

are usually correctable. All kinds of speech defects are being successfully treated. Individual instruction. Write for descriptive booklet.

SAMUEL D. ROBBINS, Director, Institute for Speech Correction
(Successor to) Boston Stammerers' Institute
Established 1867
419 Boylston St., Boston 16, Mass.

BROOKLEA FARM

A convalescent home to provide care and treatment for patients convalescing from physical illness or suffering from mild personality disorders. Medical treatment is provided by the consulting and referring staff. Psychotherapy by resident and associated psychiatrists. Nursing and dietetic needs are met by trained personnel.

Brooklea Farm is an 80-acre country estate which includes a dairy, poultry farm, vegetable and flower gardens, orchards, nursery and greenhouse and many acres under cultivation.

Patients may stroll through open fields, along shaded lanes or beside Blind Brook which flows through a wooded section of the estate. They may engage in farm activities, work in the gardens, play tennis, croquet or golf, or participate in various forms of occupational therapy.

The privileges of a private home are afforded to visitors. Relatives and friends may live at Brooklea when this is an aid to treatment.

BROOKLEA FARM
Rt. 120A, King St., Port Chester, N. Y. Tel.: Port Chester 5-0333
New York office: 11 East 71st St. Tel.: Trafalgar 9-2660

GEORGE W. HENRY, M.D.
Psychiatrist-in-charge

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 67 MAY 1952 NUMBER 5

COPYRIGHT, 1952, BY THE AMERICAN MEDICAL ASSOCIATION

CELL RESTS IN THE REGION OF THE FOURTH VENTRICLE

I. Their Site and Incidence According to Age and Sex

RICHARD J. BRZUSTOWICZ, M.D.
AND
JAMES W. KERNOHAN, M.D.
ROCHESTER, MINN.

THE RELATIONSHIP between cell rests and gliomas in certain parts of the central nervous system has been pointed out by various authors.[1] The region of the fourth ventricle, particularly its roof, has been cited as being rich in cell rests,[2] accounting for the various gliomas arising there. Cushing, in his reports on medul-

Fellow in Neurosurgery, Mayo Foundation, University of Minnesota (Dr. Brzustowicz). From the Section of Pathologic Anatomy, Mayo Clinic (Dr. Kernohan).

Partial abridgment of thesis submitted by Dr. Brzustowicz to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurosurgery.

1. (*a*) Otto, R.: Zur Hirnpathologie, Virchows Arch. path. Anat. **110**:81-94 (Oct.) 1887. (*b*) Ernst, P.: Eine Missbildung des Kleinhirns beim Erwachsenen und ihre Bedeutung für die Neubildungen, Beitr. path. Anat. **17**:547-586, 1895. (*c*) Ranke, O.: Beiträge zur Kenntnis der normalen und pathologischen Hirnrindenbildung, ibid. **47**:51-125, 1910. (*d*) Vogt, H., and Astwazaturow, M.: Über angeborene Kleinhirnerkrankungen mit Beiträgen zur Entwicklungsgeschichte des Kleinhirns, Arch. Psychiat. **49**:75-203 (Dec.) 1911. (*e*) Podmaniczky, T.: Über kongenitale Neurogliome, Frankfurt. Ztschr. Path. **5**:255-263, 1910. (*f*) Ribbert, H.: Neuroepithel in Gliomen, Zentralbl. allg. Path. **21**:145-148 (Feb.) 1910; (*g*) Über das Spongioblastom und das Gliom, Virchows Arch. path. Anat. **225**:195-213 (Aug.) 1918. (*h*) Ostertag, B.: Die typischen Geschwulstbildungen des Kleinhirns und ihre Beziehungen zu den Fehlbildungen des übrigen Medullarrohres, Klin.Wchnschr. **11**:1651-1652 (Sept. 24) 1932. (*i*) Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas, A. Research Nerv. & Ment. Dis., Proc. **16**:182-209, 1937. (*j*) Globus, J. H.: Glioneuroma and Spongioneuroblastoma, Forms of Primary Neuroectodermal Tumors of the Brain, Am. J. Cancer **32**:163-220 (Feb.) 1938; (*k*) Primary Neuroectodermal Brain Tumors: Their Transition from Benign to Malignant Forms, J. Mt. Sinai Hosp. **7**:361-382 (Jan.-Feb.) 1941. (*l*) Cushing, H.: Experiences with the Cerebellar Medulloblastomas: A Critical Review, Acta path. et microbiol. scandinav. **7**:1-86, 1930; (*m*) Experiences with Cerebellar Astrocytomas: Critical Review of 76 Cases, Surg., Gynec. & Obst. **52**:129-204 (Feb.) 1931. (*n*) Marburg, O.: Some Remarks on Tumors of the Brain in Childhood, J. Nerv. & Ment. Dis. **95**:446-459 (April) 1942. (*o*) Globus, J. H., and Kuhlenbeck, H.: Tumors of the Striatothalamic and Related Regions: Their Probable Source of Origin and More Common Forms, Arch. Path. **34**:674-734 (Oct.) 1942. (*p*) Yashkin, J. C.: Über Entwicklungsanomalien bei Kleinhirnembryonen als Grundlage pathologischer Bildungen, Arb. neurol. Inst. Wien. Univ. **31**:13-28, 1929. (*q*) Raaf, J., and Kernohan, J. W.: Relation of Abnormal Collections of Cells in Posterior Medullary Velum of Cerebellum to Origin of Medulloblastoma, Arch. Neurol. & Psychiat. **52**:163-169 (Sept.) 1944.

2. (*a*) Otto,[1a] (*b*) Ostertag,[1h] (*c*) Kernohan and Fletcher-Kernohan,[1i] (*d*) Cushing,[1l, m] (*e*) Raaf and Kernohan,[1q] (*f*) Meschede, F.: Heterotopie grauer Hirnsubstanz im Markstamme der Hemisphären des kleinen Gehirns: Drei Beobachtungen, Virchows Arch. path. Anat. **56**:82-96 (Nov.) 1872. (*g*) Pfleger, L.: Beobachtungen über Heterotopie grauer Substanz im Marke des Kleinhirns, Zentralbl. med. Wissensch. **18**:468-470 (June 26) 1880.

loblastomas in 1930 [11] and on cerebellar astrocytomas in 1931,[10b] emphasized his belief that these tumors arose from embryonal cell rests in the roof of the fourth ventricle. The Kernohans,[11] in 1935, supported a similar view for ependymomas arising in this region. Globus and Kuhlenbeck,[10] in 1942, showed that the subependymal cell plate in the region of the fourth ventricle, as well as in other parts of the brain, could be the seat of embryonal cell rests giving rise to subependymal plate gliomas.

Although many observations have been reported on the occurrence of malformations and cell rests in the region of the fourth ventricle,[3] no report of a systematic study correlating the presence of these elements and the origin of specific tumors appeared until 1944, when Raaf and Kernohan [10] showed that medulloblastomas were almost exclusively midline cerebellar tumors, because of their origin from indifferent embryonal cells lying in the posteriorly placed germinal bud of the cerebellum. As far as is known, no reports have appeared which would substantiate a similar view that gliomas of the fourth ventricle other than medulloblastomas could also have their origin in cell rests.

TABLE 1.—*Age and Sex of Patients in 253 Cases in Which the Cerebellum Was Examined*

Age Group	Sex		
	Males	Females	Total
A. Adults (20 to 100 yr.)	28	25	53
B. Children and young adults (1 to 20 yr.)	50	29	79
C. Infants (1 wk. to 1 yr.)	29	21	50
D. Infants (less than 1 wk. old)	8	7	15
E. Stillborn term infants	10	5	15
F. Premature infants (weighing more than 1,000 gm.)	25	4	29
G. Fetuses (weighing less than 1,000 gm.)	6	6	12
Total	156	97	253

MATERIAL AND METHOD OF STUDY

This study was divided into three parts. The purpose of the first part was to determine which structures in the region of the fourth ventricle were oftenest the site of cell rests. Particular attention was devoted to the roof structures, as these had been cited as being the source of most gliomas in this region. The age and sex factors also were studied in relation to the frequency of occurrence of cell rests in the region of the fourth ventricle. The second part of the study dealt with the histologic characteristics of the cell rests and was made in an attempt to explain the origin of these rests. The third part dealt with the relationship of the origin of gliomas in this region to the presence of the cell rests.

A series of 253 cerebellums fixed in a 10% solution of formalin were examined for the presence of cell rests, either heterotopic or lying in a normal position. Brains which were involved by tumors were excluded. The brains were those of adults of all ages, children, infants, and fetuses. Table 1 shows the age and sex of the patients in the 253 cases in which the cerebellum was examined. Although no selection of the specimens was made on the basis of sex,

3. Otto.[3a] Ernst.[3b] Ranke.[3c] Vogt and Astwazaturow.[3d] Ostertag.[3h] Kernohan and Fletcher-Kernohan.[11] Pfleger.[2g] Brun, R.: Zur Kenntnis der Bildungsfehler des Kleinhirns (Beitrag zur Entwicklungspathologie des Zentralnervensystems), Schweiz. Arch. Neurol. u. Psychiat. **1**:61-123, 1917; **2**:48-105; **3**:13-88, 1918.

subsequent tabulation showed that a larger number of brains was obtained from males, especially in the younger age groups, than from females.

Each cerebellum was carefully examined grossly, and blocks of tissue were prepared with particular attention to the roof structures. Sections of the anterior medullary velum and the nodulus vermis were made in the sagittal plane, while sections of the region of the posterior medullary velum were made in the parasagittal plane. Sections of the floor and the walls of the fourth ventricle were obtained in many instances, but no special effort was made to obtain as many sections of them as of the roof structures. The sections were prepared routinely and stained with hematoxylin and eosin. Slides showing cell rests were stained in many instances with cresyl violet or according to Mallory's phosphotungstic acid-hematoxylin technique. Table 2 shows the frequency with which various anatomic structures were encountered in sections prepared from the 253 cerebellums.

FREQUENCY OF CELL RESTS ACCORDING TO SITE

The region of the fourth ventricle is complex,[4] and the names and boundaries of the component parts vary considerably in different anatomic descriptions, thus adding to the complexity. In order that the site of any particular cell rest might be classified accurately, the following structures were defined: (1) the roof structures, including the anterior medullary velum, the nodulus vermis, and the paired posterior medullary vela and their continuation in the inferior medullary velum; (2) the

TABLE 2.—*Cases in Which Various Anatomic Structures in the Region of the Fourth Ventricle Were Observed in Sections*

Anatomic Structure	Cases
Anterior medullary velum	231
Posterior medullary velum	190
Nodulus	95
Ponticulus	43
Inferior medullary velum	23

ponticulus (taenia choroidea) of either side of the medulla, and the lateral walls of the fourth ventricle; (3) the cerebellar white matter and cortex, comprising the hemispheres, and (4) the floor of the fourth ventricle.

The anterior medullary velum is a thin membrane which extends from the quadrigeminal plate to the middle of the cerebellum and spans the superior cerebellar peduncles. The apex of the roof of the fourth ventricle, the fastigium, separates the anterior medullary velum from the nodulus, which is a part of the unpaired midline cerebellar vermis. The nodulus forms the inferior part of the roof of the fourth ventricle, while the anterior medullary velum forms its superior part. A thin, translucent, crescentic lamina arises from the white matter of either side of the nodulus and blends laterally with the cerebellar white matter at the edge of the

4. (*a*) Blake, J. A.: The Roof and Lateral Recesses of the Fourth Ventricle, Considered Morphologically and Embryologically, J. Comp. Neurol. **10**:79-108 (Feb.) 1900. (*b*) Ziehen, T.: Handbuch der Anatomie des Menschen: Centralnervensystem, Gustav Fischer, Jena, 1899-1903, Vol. 4, Pt. 1, pp. 479-483. (*c*) Ingvar, S.: Zur Phylo- und Ontogenese des Kleinhirns, Folia neuro-biol. **11**:205-495, 1918. (*d*) Hochstetter, F.: Über die Bedeutung einiger Namen, welche Teile der weichen Hirnhaut (Leptomeninx) und des Gehirns betreffen: 1. Tela chorioidea ventriculi tertii (superior), Tela chorioidea ventriculi quarti (inferior) und Lamina chorioidea epithelialis, Ztschr. Anat. u. Entwcklngsgesch. **101**:211-227, 1933. (*e*) Johnston, T. B.: A Note on the Peduncle of the Flocculus and the Posterior Medullary Velum, J. Anat. **68**:471-479 (July) 1934.

tonsillar recess and with the peduncle of the flocculus. These laminae are the paired posterior medullary vela, which, according to Ingvar,[40] represent the remains of a cortical continuity between the nodulus and the flocculus. The posterior medullary vela are continuous with the inferior medullary velum, which stretches between the inferior cerebellar peduncles and is attached to the ponticulus (taenia choroidea) of either side of the medulla. The inferior medullary velum is composed of two layers, the tela choroidea and the lamina tectoria of the fourth ventricle. The

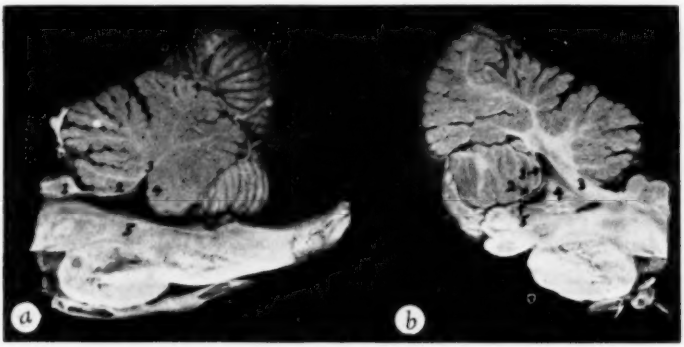


Fig. 1.—Sections of cerebellum and medulla oblongata showing relationship of various structures in region of fourth ventricle. (*a*) Sagittal section: (*1*) quadrigeminal plate, (*2*) anterior medullary velum, (*3*) fastigium, (*4*) nodulus, and (*5*) floor of fourth ventricle. (*b*) Parasagittal section: (*1*) posterior medullary velum; (*2*) inferior medullary velum, lamina tectoria of fourth ventricle; (*3*) anterior medullary velum; (*4*) wall of fourth ventricle, and (*5*) ponticulus.

TABLE 3.—*Occurrence of Cell Rests in Various Structures in the Region of the Fourth Ventricle*

Structure	Number of Sections Studied	Number of Rests	Number of Rests per 100 Sections
Cerebellar white matter	253+	35	13.8
Cerebellar cortex	...	6	2.3
Wall of fourth ventricle	...	1	....
Anterior medullary velum	234	19	8.1
Posterior medullary velum	190	12	6.3
Nodulus	95	57	60.0
Ponticulus	43	27	62.8
Inferior medullary velum	23	2	8.7

relationships and boundaries of the roof structures of the fourth ventricle are shown in Figure 1.

Cell rests were present most frequently in the nodulus and ponticulus. A total of 57 rests were found in the nodulus and of 27 rests in the ponticulus. However, considering that sections of the nodulus were obtained in 95 cases and sections of the ponticulus in 43 cases, it is evident that the frequency of cell rests occurring per 100 sections would be about the same (approximately 60 rests). The cerebellar white matter was the next most frequent site of cell rests, a total of 35 rests being found in more than 253 sections. The anterior, posterior, and inferior medullary vela had approximately the same number of rests per 100 sections examined (Table 3). It should be noted that these figures are only relative. In order that the

number of rests should be determined in any particular cerebellum, serial sections would have to be made and each section examined. The results of this study merely indicate the relative frequency of cell rests occurring in certain structures, assuming that the sections studied are representative ones.

In the adult group (Group A), the cell rests were found in the following structures, which are listed in the order of decreasing frequency of such rests: the ponticulus, the fastigial part of the anterior medullary velum, the nodulus, and the fastigial white matter. In the group from 1 to 20 years of age (Group B), a similar distribution was found, but more rests were found in the fastigial white matter than were found in this structure in Group A. In infants from 1 week to 1 year of age (Group C), cell rests occurred most frequently in the nodulus, then in the ponticulus and the cerebellar white matter. The same held true for full-term infants less than

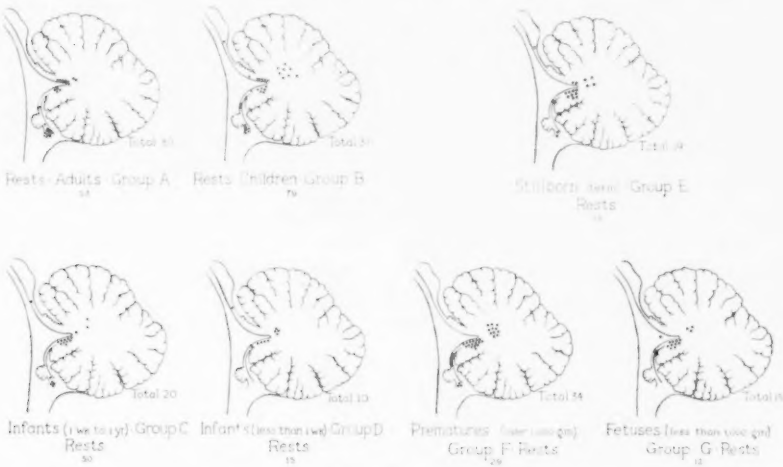


Fig. 2.—Diagrammatic sections of the cerebellum showing the site of cell rests in each of the age groups. The number of rests are indicated in the lower right-hand corner of each diagram, while the number of cases in each group is indicated under the caption. The diagrams are so drawn that in the region of the quadrigeminal plate and the anterior medullary velum the section is sagittal, while in the region of the nodulus and the posterior medullary velum it is parasagittal.

1 week old (Group D). In the last three groups (Groups E, F, and G), i. e., the stillborn term infants, the premature infants, and the fetuses, the nodulus was most frequently the site of cell rests, while the cerebellar white matter above the fastigium was next most frequently involved. The posterior and anterior medullary vela and the ponticulus were involved less frequently. The frequency with which certain structures were involved in the various age groups is shown in Figure 2.

FREQUENCY OF OCCURRENCE OF CELL RESTS IN VARIOUS AGE GROUPS

The number of cell rests in each group, as calculated per 100 cases, remained almost constant in the first four groups, i. e., from viable full-term infants to adults (Groups A, B, C, and D). In stillborn term infants (Group E), premature infants

(Group F), and fetuses (Group G), the number of rests occurring per 100 cases was about twice as great.

In the 53 adult cerebellums, 30 cell rests were found (57 rests per 100 cases). In children and young adults, 31 rests occurred in 79 cerebellums (39 rests per 100 cases). In infants from 1 week to 1 year of age, 20 rests occurred in 50 cerebellums (40 rests per 100 cases). Ten rests were found in 15 cerebellums of full-term infants less than 1 week of age (67 rests per 100 cases). In stillborn term infants, prema-

TABLE 4.—*Occurrence of Cell Rests in the Various Age Groups*

Age Group	Cases	Number of Rests	Number of Rests per 100 Cases
A. Adults (20 to 100 yr.)	53	30	57
B. Children and young adults (1 to 20 yr.)	79	31	39
C. Infants (1 wk. to 1 yr.)	50	20	40
D. Infants (less than 1 wk. old)	15	10	67
E. Stillborn term infants	15	19	127
F. Premature infants (weighing more than 1,000 gm.)	29	34	117
G. Fetuses (weighing less than 1,000 gm.)	12	15	125

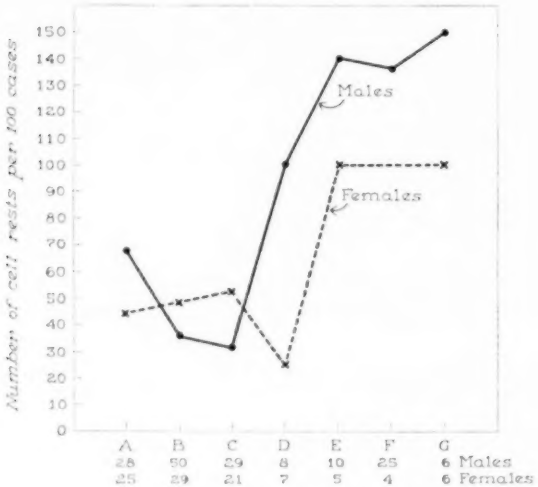


Fig. 3.—Incidence of cell rests per 100 cases in each of the age groups. Below each age group (*A*, *B*, *C*, *D*, *E*, *F*, and *G*) the number of males and females is indicated.

ture infants, and fetuses, 19 cell rests occurred in 15 cases, 34 cell rests in 29 cases, and 15 rests in 12 cases, respectively. Expressed in terms of the number of rests per 100 cases, the frequency for the last three groups was 127, 117, and 125 (Table 4).

FREQUENCY OF OCCURRENCE OF CELL RESTS IN THE TWO SEXES

An analysis of the number of cell rests occurring in the two sexes in the various age groups revealed that in the adult group (Group A) slightly more rests were found in the cerebellums of males than of females. In infants 1 week of age or older,

and in children and young adults (Groups B and C), slightly more rests were found in females than in males. In infants less than 1 week of age, in stillborn term infants, and in premature infants and fetuses (Groups D, E, F, and G), the males consistently showed a greater number of cell rests than the females (Fig. 3). Whether the difference in the incidence of cell rests in the two sexes in the earlier age groups is significant is difficult to state. It is evident that in this series a large number of males was compared with a smaller number of females, and this may be the basis of the difference in the frequency of occurrence of cell rests in the two sexes.

SUMMARY

Two hundred fifty-three cerebellums, not involved by tumors, were examined for the presence of cell rests. The ponticulus and cerebellar nodulus were the most frequent sites of cell rests. The cerebellar white matter was involved less frequently, while the anterior, posterior, and inferior medullary vela were involved least frequently. Cell rests occurred most frequently in stillborn term infants, premature infants, and fetuses. The incidences of rests in the cerebellums of adults, children, and infants were approximately the same. The frequency of occurrence of rests in males was greater than in females in term infants less than 1 week of age, in stillborn term infants, in premature infants, and in fetuses. In the older age groups, there was little difference in the frequency of rests in males and in females.

Because the roof structures have been thought to be the site of numerous cell rests, many authors have ascribed the origin of tumors involving the fourth ventricle to these rests. The results of this study indicate that the ponticulus of the medulla, forming the most inferior border of the fourth ventricle, contains as many cell rests as, or more than, the nodulus, which forms part of the posterior vermis of the cerebellum.

CELL RESTS IN THE REGION OF THE FOURTH VENTRICLE

II. Histologic and Embryologic Consideration

RICHARD J. BRZUSTOWICZ, M.D.
AND
JAMES W. KERNOHAN, M.D.
ROCHESTER, MINN.

CELL RESTS in the region of the fourth ventricle are found most frequently in fetuses and premature and stillborn infants.[1] The frequencies of occurrence of rests after birth are relatively the same in the three groups. Cell rests are found predominantly in the ponticulus of the medulla oblongata and the nodulus of the cerebellum. The cerebellar white matter is the next most frequent site of cell rests, while the anterior, posterior, and inferior medullary vela are involved less frequently.

When studied histologically, cell rests show variation in cellular composition, in the degree of cellular differentiation, and in the degree of organization. Brun,[2] in reporting the results of his study of malformations of the cerebellum in 1917 and 1918, pointed out that cellular elements which are dislocated from their normal position and which have no recognizable architectural pattern should be designated as "heterotaxic," while the term "heterotopic" should be reserved for those dislocated elements with a definite architectural form.

CLASSIFICATION OF CELL RESTS

According to their cellular composition, cell rests occurring in the region of the fourth ventricle may be classified as follows: mixed-cell rests, ependymal-cell rests, rests of the external granular layer, and neuronal rests.

Mixed-Cell Rests.—There are at least two types of mixed-cell rests. One type is poorly organized, while the other is the well-organized heterotopia of the cere-

From the Section of Pathologic Anatomy, Mayo Clinic (Dr. Kernohan).

Fellow in Neurosurgery, Mayo Foundation, University of Minnesota (Dr. Brzustowicz).

Partial abridgment of thesis submitted by Dr. Brzustowicz to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurosurgery.

1. Brzustowicz, R. J., and Kernohan, J. W.: Cell Rests in the Region of the Fourth Ventricle: I. Their Site and Incidence According to Age and Sex, A. M. A. Arch. Neurol. & Psychiat., this issue, p. 585.

2. Brun, R.: Zur Kenntnis der Bildungsfehler des Kleinhirns (Beitrag zur Entwicklungspathologie des Zentralnervensystems): I. Über Aplasie und Hypoplasie des Neozerebellums; zugleich ein Beitrag zur Lehre von den Kleinhirnanteilen, Schweiz. Arch. Neurol. u. Psychiat. **1**:61-123, 1917; II. Epikritische Bemerkungen zur Entwicklungspathologie, Morphologie und Klinik der umschriebenen Entwicklungshemmungen des Neozerebellums, ibid. **2**:48-105, 1918; III. Über niedere Entwicklungshemmungen (Agenesie und Amorphogenesis) der Gesamtanlage des Kleinhirns, ibid. **3**:13-88, 1918.

bellar cortex described by many investigators.[3] The former type occurs more commonly and is usually found in the nodulus or in the white matter just above the fastigium. The cortical rests may occur in the fastigial white matter but oftener are found in the folial white matter.

The mixed rests of the first type consist of neurons, astrocytes, oligodendrocytes, granule cells, deeply staining elongated cells resembling medulloblasts, and blood vessels, in varying proportions. Usually, there is a capillary network which is richer than that in the tissue surrounding the heterotopic area. The cells are scattered, without any pattern, and are not sharply delimited from the rest of the white matter. Occasionally, definite islands or canaliculi of ependymal cells are present in these areas of mixed cells. These rests give the general impression that they are rather poorly differentiated and immature. They usually occur in the cerebellums of young persons and children, but most frequently in premature infants and fetuses (Fig. 1*a* and *b*).

Heterotaxic areas of mixed, disorganized elements were found in the fastigial white matter of 59 of the 253 cerebellums studied. These consisted of scattered neurons, astrocytes, oligodendrocytes, medulloblast-like cells, and capillaries, which were not as compact as in the heterotopic groups described. These heterotaxic areas were found only in the cerebellums of adults, children, and infants more than 1 week of age.

The cortical heterotopias which are found in the region of the fourth ventricle have the appearance of islands of cerebellar cortex which have been somehow cut off from the surface. These masses are circumscribed and have a definite structure. The outermost layer consists of a ring of granule cells and astrocytes. Purkinje cells may be observed scattered between the granule cells and the surrounding cerebellar white matter. These heterotopic rests vary in size from those which are visible grossly as elongated, round, or oval masses of gray matter in the deeper white matter to those which can only be seen microscopically.[3c] These cortical masses are usually found in the cerebellums of adults and young people, and infrequently in the fetuses and newborn infants (Fig. 1*c* and *d*).

Ependymal-Cell Rests.—Rests of this type are next most frequently seen. These consist of typical ependymal cells with moderately large, oval, vesicular nuclei. The heterotopic cells usually form small clusters, islands, canals, or acinar structures beneath the ependymal surface lining the fourth ventricle. At times it is difficult to determine whether a certain ependyma-lined canal is really heterotopic or whether it represents the cross section of a deep invagination from the normal ependymal surface. However, in most cases, serial sections reveal that these structures have no connection with the surface ependymal layer.

In our study, ependymal-cell rests were seen most frequently in the region of the ponticulus. In the anterior medullary velum, the ependymal-cell rests usually were found at either the junction of the anterior medullary velum and the quadrigeminal

3. (*a*) Brun.[2] (*b*) Meschede, F.: Heterotopie grauer Hirnsubstanz im Markstamme der Hemisphären des kleinen Gehirns: Drei Beobachtungen, Virchows Arch. path. Anat. **56**:82-96 (Nov.) 1872. (*c*) Pfleger, L.: Beobachtungen über Heterotopie grauer Substanz in Marke des Kleinhirns, Zentralbl. med. Wissensch. **18**:468-470 (June) 1880. (*d*) Otto, R.: Zur Hirnpathologie, Virchows Arch. path. Anat. **110**:81-94 (Oct.) 1887. (*e*) Ranke, O.: Beiträge zur Kenntnis der normalen und pathologischen Hirnrindenbildung, Beitr. path. Anat. **47**:51-125, 1910.

plate or at the fastigial end, where the ependymal lining is usually thrown into several transverse corrugations (Fig. 2*a*). The nodulus (Fig. 2*c* and *d*) and the posterior (Fig. 2*b*) and inferior medullary vela were also found to have ependymal-cell rests, but not to the extent seen in the ponticulus or the anterior medullary

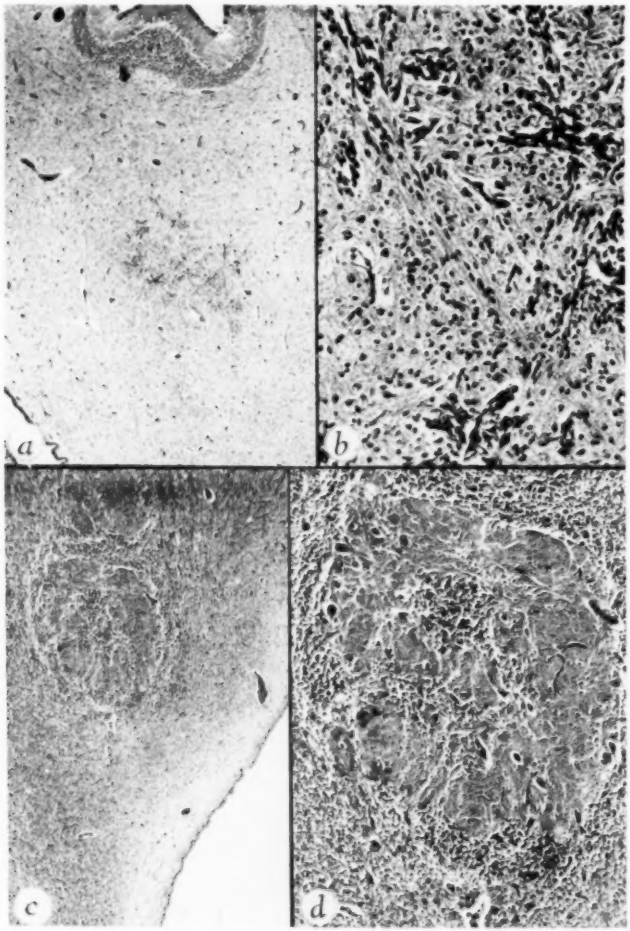


Fig. 1.—(*a* and *b*) Mixed-cell rest in white matter in region of fastigium of cerebellum of a male infant: (*a*) section stained with hematoxylin and eosin (×26); (*b*) higher magnification of section in *a* (×160), showing deeply staining, elongated cells (*c* and *d*). Heterotopic cortical rest in region of fastigium of a girl aged 4½ years: (*c*) section stained with hematoxylin and eosin (×26); (*d*) higher magnification of section in *c* (×70).

velum. The floor of the fourth ventricle in the region of the longitudinal median furrow and at the point of junction with the cerebral aqueduct contained numerous

ependymal islands, nests, and blind canaliculi. These have been described by Spiller, de Lange, Roback and Gerstle, and Marburg, as mentioned in the article by Russell.[4]

The ependymal-cell rests show variation in their degree of differentiation. This is usually in keeping with the age of the person. In fetuses or young children the

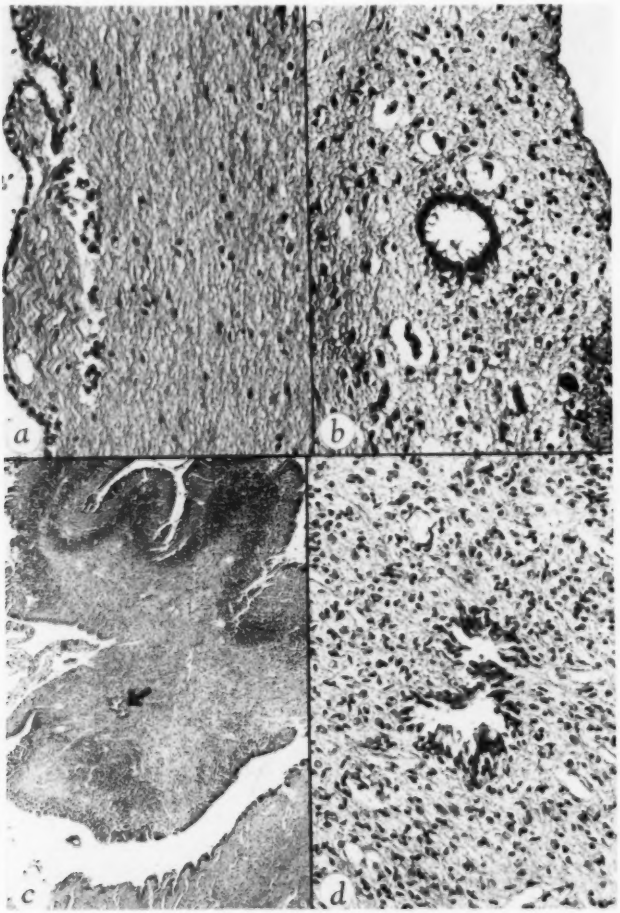


Fig. 2.—(*a*) Ependymal-cell rests in region of fastigium of anterior medullary velum of a boy aged 14 (hematoxylin-eosin stain; × 150); (*b*) ependymal-cell rests in posterior medullary velum of a male infant born dead at term (hematoxylin-eosin stain; × 185); (*c*) ependymal-cell rests (indicated by arrow) in nodulus of cerebellum of a premature, stillborn male infant (hematoxylin-eosin stain; × 30); (*d*) higher magnification of section shown in *c* (× 185).

4. Russell, D. S.: Observations on the Pathology of Hydrocephalus, Special Report Series 265, Medical Research Council, London, 1949.

cerebellums contain islands and canals of ciliated ependymal cells. The nuclei of these cells are darker and larger than those of the cells forming rests in the older age groups. Rests of ependymal cells were found to occur to about the same degree in all age groups but the fetal group. This discrepancy may be due to the relatively small number of cerebellums examined in the latter age group.

External-Granular-Layer Rests.—These rests are remnants of the external granular layer of the cerebellum, which is present in fetal life and shortly thereafter.[5] They consist of circumscribed, compact sheets or islands of small cells with deeply staining, oval nuclei. These cell rests are usually found beneath

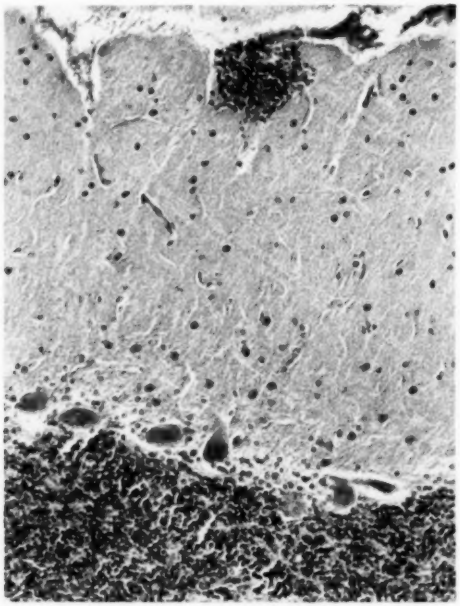


Fig. 3.—Rest of the external granular cell layer on the surface of a cerebellar folium in a man aged 42 (hematoxylin-eosin stain; × 150).

the pia-mater on the surface of a folium, or there may be a thin layer of cortex overlying the island of granule cells (Fig. 3). There may also be a diffuse scattering of these cells from the folial surface, through the molecular layer down to the internal granule cells.[2] These are the heterotaxic areas which Brun described in 1917 and 1918. We found six external-granule-cell rests in our study. Four occurred in adults, one in a 3-year-old girl, and one, in an 11-month-old girl.

5. Raaf, J., and Kernohan, J. W.: A Study of the External Granular Layer in the Cerebellum: Disappearance of the External Granular Layer and the Growth of the Molecular and Internal Granular Layers in the Cerebellum, Am. J. Anat. **75**:151-172 (Sept.) 1944.

Neuronal Rests.—These rests consist of a compact island of neurons not arranged in any definite pattern, and in no way resembling any of the organized nuclear masses seen in the region of the fourth ventricle. Only one such rest was observed in our study. A definite circumscribed mass of closely packed young neuronal elements was seen lying beneath the dentate eminence of the wall of the fourth ventricle (Fig. 4). The dentate nucleus appeared well formed and lay more laterally. The cells of the rest were round and had large vesicular nuclei, containing deeply staining nucleoli and Nissl bodies. No similar structures were seen in sections of this region of any of the cerebellums used in this study. This rest was found in a male fetus of 6 months.

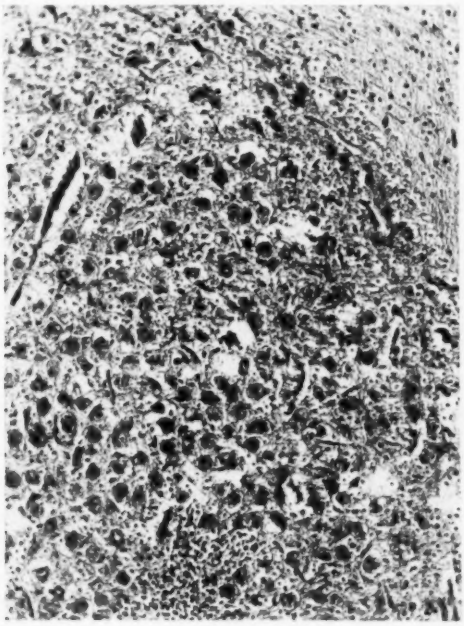


Fig. 4.—Neuronal-cell rest in white matter of cerebellum of a male infant born alive at the sixth month of gestation (hematoxylin-eosin stain; × 110).

DEVELOPMENT OF THE CEREBELLUM

The neural groove is formed in the median line of the germinal plate of embryos from 1 to 2 weeks of age. Subsequently, the edges of the groove grow upward and approach each other and fuse to form the neural tube. While still in the neural-plate stage, the central nervous system differentiates into an anterior part, which eventually forms the brain, and a posterior part, which forms the spinal cord. About the third week, the neural tube bends at its anterior end to form the cephalic flexure, in the region of the midbrain. The walls of the tube, especially in the region of the rhombencephalon, show definite variations in thickness. At about the end of the fourth week, the pontine and cervical flexures begin to appear and

produce a relative shortening of the cephalic neural tube on itself.[6] With the appearance of these flexures, definite changes occur in the roof of the cavity of the rhombencephalon.

At about the end of one month, this cavity, the fourth ventricle, assumes an elongated rhomboidal shape. Because of the pontine flexure, the thin roof is drawn out transversely, and a fold, the plica choroidea, is produced.[7] This is the forerunner of the choroid plexus of the fourth ventricle.[8] During the second month, the alar plates of the rhombencephalon rapidly thicken, arch over the fourth ventricle, and approach each other. Because of this growth, the rhombic lip (the point from which the roof plate comes off the alar plate) is folded back on itself and becomes partly fused. During the third month, the cerebellar plates are fused only rostrally, at the point of their attachment to the anterior medullary velum. They then begin to fuse across the midline on the dorsal surface rostrally, and later fuse posteriorly and ventrally. At this time, the cerebellar mass also begins to grow outward and in length, so that the surface is thrown into folds. Near the midline, ventrally, on each side, a swelling appears, which corresponds to the vermis. The rhombic lip lying along the posterior part of the cerebellar mass enters into the formation of the nodulus, the posterior and lateral medullary vela, and the flocculus. Further development of the cerebellum takes place during the fourth and fifth months to produce the appearance seen in the adult.[9]

Histologically, the cerebellar neuronal elements are the basket and star cells in the molecular layer, the Purkinje cells, and the granule cells. The neuroglial elements include oligodendrocytes, found diffusely in all layers, and protoplasmic astrocytes, found in the granule-cell layer. In addition, there are two types of astrocytes which occur specifically in the cerebellar cortex. One of these is the Golgi epithelial cell; the other is the Fañanás cell.[10]

Embryologically, the alar plates, from which the cerebellum arises, have at the onset the typical ependymal, mantle, and marginal zones found in the rest of the neural tube.[11] At the end of the second month, the line of demarcation between the ependymal and the mantle zone is poorly defined. Later, the ependymal layer of the cerebellar plates appears less active, but that situated at the rhombic lip undergoes active proliferation until late in embryonic life. From about the third month, the cells in this germinal region proliferate and migrate over the entire external surface of the cerebellum, forming a sheet of cells which becomes the external granular layer. This layer may persist for 18 to 20 months after birth.[5] From the earliest

6. Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1910-1912.

7. Blake, J. A.: The Roof and Lateral Recesses of the Fourth Ventricle, Considered Morphologically and Embryologically, J. Comp. Neurol. **10**:79-108 (Feb.) 1900.

8. Haller, G.: Über den Bau und die Entwicklung der Deckplatte des vierten Ventrikels, insbesondere beim Menschen, Verhandl. Anat. Gesellsch. Erlangen **31**:123-136, 1922.

9. Bradley, O. C.: The Mammalian Cerebellum: Its Lobes and Fissures, J. Anat. **39**:99-117 (Oct.) 1904. Ingvar, S.: Zur Phylo- und Ontegenese des Kleinhirns, Folia neuro-biol. **11**:205-495, 1918. Hochstetter, F.: Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns, Vienna, Franz Deuticke, 1929.

10. Kershman, J.: The Medulloblast and the Medulloblastoma: A Study of Human Embryos, Arch. Neurol. & Psychiat. **40**:937-967 (Nov.) 1938.

11. Keith, A.: Human Embryology and Morphology, Ed. 6, Baltimore, Williams & Wilkins Company, 1948, pp. 133-155.

time of its formation, a constant flow of cells occurs from the external granular layer into the substance of the cerebellum. Schaper,[12] in 1894, postulated that these cells were bipotential and gave rise to both neuronal and astrocytic elements. Kershman [10] confirmed this concept in 1938. The dentate and other nuclei of the cerebellum are formed from the germinal epithelium lining the cavity of the fourth ventricle.

MODE OF ORIGIN OF CELL RESTS

This study raised certain questions as to the origin of cell rests in the region of the fourth ventricle. Why did rests of a certain histologic type occur only in certain sites? Why were certain structures involved by rests more frequently than other structures? Why did some structures, such as the nodulus, contain rests of a more primitive or germinal character than did other parts? The answers to these questions could only be provided by examining in detail certain processes in the development of the cerebellum and the structures in the region of the fourth ventricle.

Cell rests, it appeared, could occur whenever the following processes occurred in the developmental history of the cerebellum: (1) a folding or bending of a cell layer on itself; (2) fusion of several cell layers; (3) arrest in the migration of germinal elements from the germinal epithelium lining the cavity of the fourth ventricle, or from the external granular layer, and (4) an alteration or derangement of the normal process of differentiation of germinal cells.

Rests Resulting from a Folding or Bending of Cell Layers.—At about the end of the fourth week of embryonic life the formation of the pontine and cervical flexures produces a deep fold in the floor of the fourth ventricle near the opening of the cerebral aqueduct. This deep transverse furrow is well seen in sagittal sections of the fetal brain stem (Fig. 5). Older brains contain numerous ependymal islands, canals, and acini, which represent the remnants of this cleft. The junction of the anterior medullary velum and the quadrigeminal plate at the point of decussation of the trochlear nerves is also subjected to folding and stretching and may contain many isolated ependymal islands and canaliculi beneath the surface ependymal layer. This region also frequently is the site of hyperplasia of the ependymal lining, as well as of subependymal gliosis.

Where a furrow or cleft occurs, islands of ependymal cells can be pinched off by glial proliferation on either side of the cleft. This process probably accounts for the ependymal islands and acini found beneath the ependymal layer lining the fastigial portion of the anterior medullary velum. Here the ependymal layer is thrown into several transverse corrugations before covering the superior surface of the nodulus. Similarly, the ependymal rests found beneath the longitudinal median furrow of the floor and of the inferior surface of the anterior medullary velum can be explained in this way.

Rests Resulting from Fusion of Cell Layers.—At the time that the embryonal cerebellar plates rapidly enlarge (during the second month), the rhombic lip folds back on itself and becomes partly fused. It is this part which becomes the ponticulus of the hindbrain of the adult and which contains numerous ependymal-cell rests. These are formed by the fusion of layers of germinal ependymal cells; and islands, canals, and acini are formed by subsequent glial proliferation.

12. Schaper, A.: Die morphologische und histologische Entwicklung des Kleinhirns der Teleostier, Morphol. Jahrb. **21**:625-705 (Sept.) 1894.

Rests Resulting from Arrested Migration of Germinal Elements.—Rests and heterotaxic groups of mixed cells lying in the fastigial white matter occur frequently. These might be explained as resulting from an arrest in the migration of germinal cells from the primitive layer lining the roof of the fourth ventricle to the sites of the cerebellar roof nuclei or to the cerebellar cortex. However, these rests can be explained in another way. Early in embryonic life there is a definite cerebellar ventricle, which is formed when the paired cerebellar-plate anlagen join over the fourth ventricle. This ventricle is connected by means of a canal to the fourth ventricle. Yaskin,[13] in 1929, reported that this canal was still evident in human embryos of 20 cm. crown-rump length. Undoubtedly, the germinal cell layers lining the cerebellar canal and ventricle could account for the presence of these mixed rests in the fastigial and folial white matter.

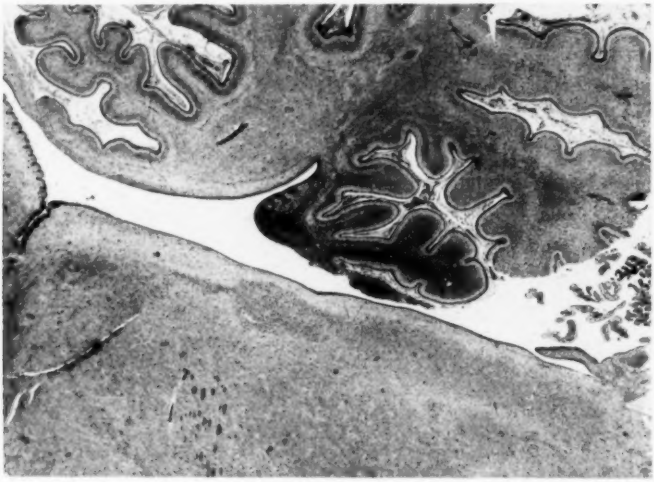


Fig. 5.—Parasagittal section of cerebellum of a male infant born dead at the sixth month of gestation. The section shows a deep transverse cleft at the anterior end of the fourth ventricle, scalloping of the floor in the region of the aqueduct, and streaming of germinal cells in a sheet from the nodular-velar region (stained with hematoxylin and eosin; × 10).

Rests of the external granular layer on the folial surface of the cerebellum can be explained by the persistence of these cells beyond the time normally required for their inward migration and differentiation. Raaf and Kernohan,[5] in 1944, demonstrated that the external granular cell layer could persist for 18 to 20 months postnatally.

Rests Resulting from Alteration or Disturbance in the Differentiation of Germinal Cells.—Although the modes of origin discussed above account for the formation of cell rests of many varieties, they do not explain the rests found in the region of the nodulus. It is interesting to note that the majority of cell rests occur in the nodulus, which is a derivative of the most primitive part of the cerebellum, the archi-

13. Yaskin, J. C.: Über Entwicklungsanomalien bei Kleinhirnembryonen als Grundlage pathologischer Bildungen, Arb. neurol. Inst. Wien. Univ. **31**:13-28, 1929.

cerebellum. The nodulus, the posterior medullary velum, the flocculus, and the lateral medullary velum can be considered as a unit because of their common origin from the posterior rhombic lip of the paired cerebellar plates. This region is unique in that there is an intense proliferation of germinal elements which cover the surface of the cerebellum during embryonic life. In other parts of the central nervous system, the germinal epithelial layer lining the neural tube provides the neuronal and glial elements. It is in this region derived from the posterior rhombic lip that a variety of rests in all degrees of differentiation can be found, but particularly in the central nodular portion. Ependymal-cell rests occur all along this border strip, but not to as great an extent as at the anterior end of the anterior medullary velum or the ponticulus. The nodulus is most frequently the site of islands of neurons, astrocytes, granule cells, oligodendrocytes, deeply staining, carrot-shaped cells, and blood vessels, arranged in a haphazard way. The posterior medullary velum may contain similar mixed rests, but more frequently definite islands or extensions of cerebellar cortex from either the nodulus or the flocculus may be found on its surface. These should not be considered as heterotopic, because they represent remnants of the original cortical connection between the nodulus and the flocculus.[14]

The frequent presence of mixed rests in the nodulus can be accounted for only by the persistence of germinal elements and a subsequent arrest at some point in the differentiation and organization of these elements. How else can the presence of Purkinje cells, oligodendrocytes, astrocytes, and medulloblast-like cells without any orderly arrangement be explained?

SUMMARY

On the basis of their cellular composition, cell rests occurring in the region of the fourth ventricle may be classified as follows: (1) mixed-cell rests; (2) ependymal-cell rests; (3) rests of the external granular layer, and (4) neuronal rests.

In our study of 253 cerebellums, mixed-cell rests were encountered most frequently. A large variation in the degree of differentiation of these rests was noted. The highly organized heterotopia of the cerebellar cortex occurred in the older age groups and was much less frequent than the poorly organized mixed-cell rests. It occurred either in the fastigial or in the folial white matter. The less differentiated, poorly organized mixed-cell rests, with varying numbers of germinal elements, were most frequently found in premature infants and fetuses. These rests occurred oftenest in the nodules and, to a less degree, in the fastigial white matter.

The ependymal-cell rests occurred next most frequently. These were found in the cerebellums of 20 to 50% of all age groups except the fetal group. The rests occurred oftenest in the ponticulus and the anterior medullary velum. They had a more immature histologic appearance in the younger age groups.

Rests of the external granular layer were found in six cases. Four were found in adults. These rests were situated on the surface of a cerebellar folium and appeared as a circumscribed sheet or island of cells. Only one rest consisting entirely of neuronal elements was observed in this study.

14. Raaf and Kernohan.[5] Jaksche, H.: Beobachtungen über Oberflächenverhältnisse im Bereiche und in der Umgebung des Velum medullare posterius (cerebellare), Morphol. Jahrb. **77**:273-304 (March) 1936. Langelaan, J. W.: On the Development of the External Form of the Human Cerebellum, Brain **42**:130-170 (June) 1919. Johnston, T. B.: A Note on the Peduncle of the Flocculus and the Posterior Medullary Velum, J. Anat. **68**:471-479 (July) 1934.

CELL RESTS IN THE REGION OF THE FOURTH VENTRICLE

III. Their Relationship to the Development of Gliomas

RICHARD J. BRZUSTOWICZ, M.D.
AND
JAMES W. KERNOHAN, M.D.
ROCHESTER, MINN.

TUMORS involving the fourth ventricle have been studied intensively by various investigators [1] since Balme-Degarray first reported such a case in 1836.[2] With the impetus provided by the development of neurosurgery after the turn of the century, reports of a large number of cases were accumulated, permitting certain generalizations to be made regarding tumors involving the fourth ventricle. These may be briefly summarized as follows: Tumors in this region occur most commonly in children and young adults. The commonest tumors involving this region are astrocytomas, medulloblastomas, and ependymomas. The medulloblastomas occur in the midline in the posterior part of the roof of the fourth ventricle [3]; the astrocytomas usually occur in the midline,[4] but may also lie laterally and extend into the cerebellar hemisphere.[5] The ependymomas, too, usually occur in the midline of the roof, but may occur laterally or arise from the floor of the fourth ventricle.

That all the medulloblastomas and the majority of the ependymomas should arise in such a circumscribed area stimulated much interest and conjecture as to the reasons for this occurrence. It was the opinion of such investigators as Yaskin,[6]

From the Section of Pathologic Anatomy, Mayo Clinic (Dr. Kernohan).
Fellow in Neurosurgery, Mayo Foundation, University of Minnesota (Dr. Brzustowicz).

Partial abridgment of thesis submitted by Dr. Brzustowicz to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurosurgery.

1. Brüning, H.: Zur Kasuistik der Tumoren im 4. Ventrikel, Jahrb. Kinderh. **55**:647-666, 1902. Martens, M., and Seiffer, W.: Zur Pathologie der Kleinhirngeschwülste (multiple ependymare Gliome), Berl. klin. Wchnschr. **2**:1477-1481 (Aug. 10) 1908. Bassoe, P.: Tumors of the Third and Fourth Ventricles, J. A. M. A. **67**:1423-1428 (Nov. 11) 1916. Bergstrand, H.: Über das sog. Astrocytom im Kleinhirn, Virchows Arch. path. Anat., **287**:538-548 (Dec.) 1932. Lereboullet, J.: Les tumeurs du quatrième ventricule: étude anatomoclinique et therapeutique, Paris, J. B. Baillière et fils, 1932. Cimbal, W.: Beiträge zur Lehre von den Geschwülsten im 4. Ventrikel, Virchows Arch. path. Anat. **166**:289-316 (Nov.) 1901. Lereboullet, J.: Les tumeurs du IVe ventricule: Étude clinique, Paris méd. **99**:73-83 (Jan. 25) 1936; Formes anatomiques diagnostic et traitement, ibid. **99**:161-176 (Feb. 22) 1936. Craig, W. M., and Kernohan, J. W.: Tumors of the Fourth Ventricle, J. A. M. A. **111**:2370-2377 (Dec. 24) 1938.

2. Balme-Degarray, A., cited by Spillmann, P. and Schmitt, J.: Contribution à l'étude des tumeurs du quatrième ventricule, Arch. gén. de méd. **150**:182-205, 1882.

3. Cushing, H.: Experiences with the Cerebellar Medulloblastomas: A Critical Review, Acta path. et microbiol. scandinav. **7**:1-86, 1930.

4. Cushing, H.: Experiences with Cerebellar Astrocytomas: Critical Review of 76 Cases, Surg., Gynec. & Obst. **52**:129-204 (Feb.) 1931.

5. Bucy, P. C., and Gustafson, W. A.: Structure, Nature and Classification of the Cerebellar Astrocytomas, Am. J. Cancer **35**:327-353 (March) 1939.

6. Yaskin, J. C.: Über Entwicklungsanomalien bei Kleinhirnembryonen als Grundlage pathologischer Bildungen, Arb. neurol. Inst. Wien. Univ. **31**:13-28, 1929.

Cushing,[7] Ostertag,[8] the Kernohans,[9] and Globus and Kuhlenbeck[10] that these tumors arose from embryonic rests in the roof of the fourth ventricle. Raaf and Kernohan[11] showed that the medulloblastoma was exclusively a midline cerebellar tumor because it probably arose from rests of indifferent embryonal cells lying in the germinal bud of the cerebellum.

The study on which this report is based was undertaken in an attempt to determine the sites of predilection of gliomas, other than medulloblastomas, involving the fourth ventricle and to correlate them with the sites of predilection of cell rests of a particular histologic type.

MATERIALS AND METHOD OF STUDY

Seventy-nine cases of glioma involving the fourth ventricle, exclusive of medulloblastomas, were used in this study. Only cases in which necropsy was performed were used, so that the region of the fourth ventricle could be examined grossly as carefully as possible, the site of the tumor exactly described, and its probable site determined. Blocks of tumor and adjacent brain tissue were obtained in each case, and histologic sections were prepared to aid in localizing the site of origin of the tumor. The sections were stained with hematoxylin and eosin or by the Mallory phosphotungstic acid-hematoxylin technique.

TABLE 1.—*Site of Origin of Ependymomas Involving the Fourth Ventricle*

Site	Number
Wall of the ventricle	18
Nodulus	15
Ponticulus	4
Floor of the ventricle	4
Posterior medullary velum	1
Anterior medullary velum	1
Total	43

In many instances the tumor filled the fourth ventricle completely or had been almost completely removed surgically prior to death. Since the confines of the fourth ventricle are limited and various structures, such as the nodulus, the anterior and posterior medullary vela, and the ventricular wall, lie within 1 cm. of one another, they are greatly distorted, stretched, or involved by tumor tissue. In such cases the exact site of tumor origin had to be reconstructed and assigned on the basis of probability.

RESULTS

Of the 79 gliomas involving the fourth ventricle, 43 were ependymomas, 23 astrocytomas, and 13 subependymal-plate gliomas. In the cases of ependymoma, the wall of the fourth ventricle and the nodulus were oftenest assigned as probable sites of tumor origin (Table 1). The ponticulus and the floor of the fourth ventricle

7. Footnotes 3 and 4.

8. Ostertag, B.: Die typischen Geschwulstbildungen des Kleinhirns und ihre Beziehungen zu den Fehlbildungen des übrigen Medularohres, Klin. Wchnschr. **11**:1651-1652 (Sept. 24) 1932.

9. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas: A Study of 109 Cases, A. Res. Nerv. & Ment. Dis., Proc. **16**:182-209, 1937.

10. Globus, J. H., and Kuhlenbeck, H.: The Subependymal Cell Plate (Matrix) and Its Relationship to Brain Tumors of the Ependymal Type, J. Neuropath. & Exper. Neurol. **3**:1-35 (Jan.) 1944.

11. Raaf, J., and Kernohan, J. W.: Relation of Abnormal Collections of Cells in Posterior Medullary Velum of Cerebellum to Origin of Medulloblastoma, Arch. Neurol. & Psychiat. **52**:163-169 (Sept.) 1944.

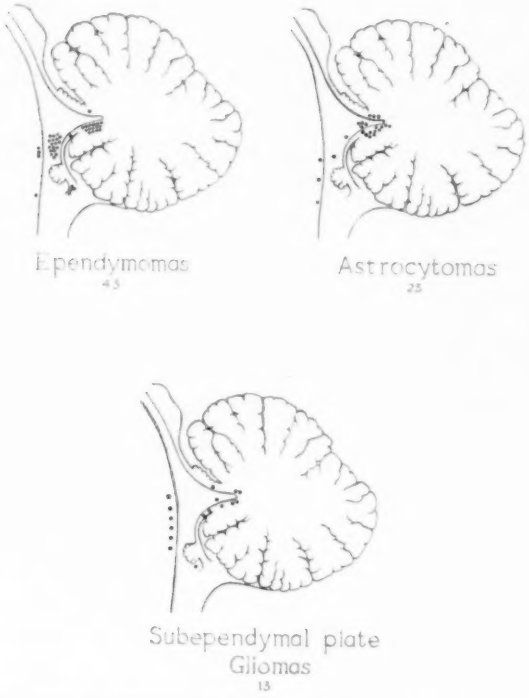


Fig. 1.—Diagrammatic sections of cerebellum showing the probable sites of origin of astrocytomas, ependymomas, and subependymal gliomas in the region of the fourth ventricle. The number of cases in each group is indicated under the caption.

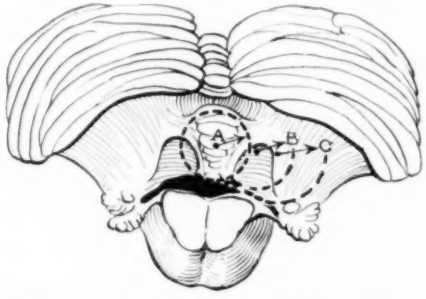


Fig. 2.—Ventral view of midline structures of the cerebellum. Dotted arcs *A* (nodulus), *B*, (posterior medullary velum), and *C* (flocculonodular ansa) indicate the possible sites of origin of tumors. These tumors grow into the fourth ventricle and can be considered as tumors of the posterior vermis.

were considered the next most frequent sites (Fig. 1). The posterior and anterior medullary vela were considered the least frequent sites, probably because these structures were usually completely involved by tumor tissue and not identified. The nodulus, the posterior medullary velum, and the adjacent wall of the fourth ventricle lie in the same immediate vicinity, and it is possible that a tumor arising in the

Fig. 3.—Transverse section of the cerebellum showing cellular ependymoma, Grade 2, of the posterior vermis (hematoxylin-eosin stain; × 6).

TABLE 2.—*Site of Origin of Astrocytomas Involving the Fourth Ventricle*

Site	Number
Nodulus	11
Wall of the ventricle	6
Anterior medullary velum	3
Floor of the ventricle	3
Total	23

velum could be assigned to the nodulus or the wall when seen as a mass several centimeters in diameter. Figure 2 illustrates how tumors arising in this region are grossly classified as posterior-vermis tumors and the reason for the difficulty of assigning a definite site of origin for such a tumor (Fig. 3).

In the cases of astrocytoma, the nodulus was considered to be most frequently the site of origin, and the wall of the fourth ventricle was considered the next most frequent site of origin (Table 2). The floor of the fourth ventricle and the anterior

medullary velum were involved less often. Astrocytomas which occurred definitely in the cerebellar hemispheres and which were not related to the fourth ventricle were not included in this study (Fig. 4).

Subependymal-plate gliomas arose most frequently from the floor of the fourth ventricle (Table 3). They arose with approximately the same frequency from the nodulus and the velar structures (Fig. 5). In one case multiple tumors arose from

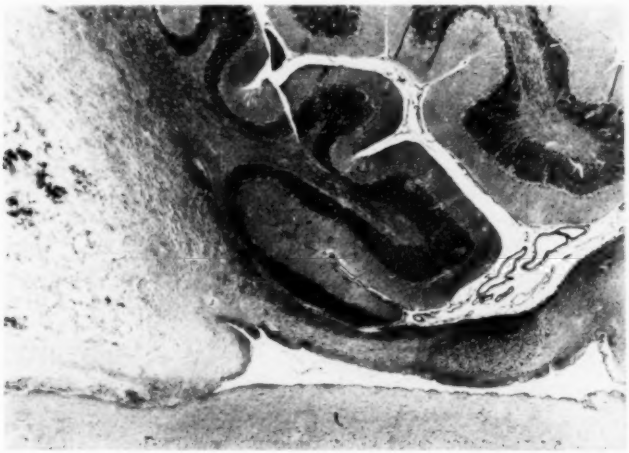


Fig. 4.—Parasagittal section of cerebellum showing a fibrillary astrocytoma, Grade 2, of the posterior vermis. This section shows the relation of the anterior medullary velum and the floor of the fourth ventricle to the tumor occupying the nodulus (hematoxylin-eosin stain; × 10).

TABLE 3.—*Site of Origin of Subependymal-Plate Gliomas Involving the Fourth Ventricle*

Site	Number
Floor of the ventricle	6
Nodulus	3
Anterior medullary velum	3
Posterior medullary velum	2
Wall of the ventricle	2
Total	16 *

* A total of 16 sites of origin was listed for 13 cases. In one case, tumors arose from four sites.

the anterior and posterior medullary vela, the nodulus, and the floor of the fourth ventricle.

Incidence According to Sex.—Of the 43 patients with ependymomas, 27 were males and 16 females. Of 23 patients with astrocytoma, 12 were males and 11 females, and of 13 patients with subependymal-plate glioma, 11 were males and 2 females.

Incidence According to Age.—The majority of patients with ependymoma or astrocytoma were in the first two decades of life. In the cases of subependymal-plate glioma, there was a tendency to a more even distribution in the various age groups (Fig. 6).

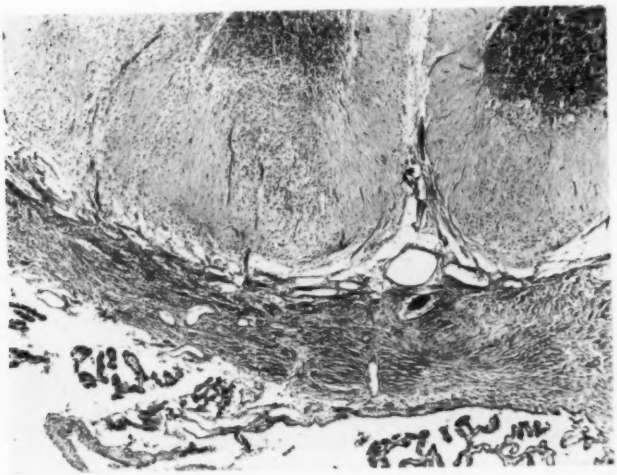


Fig. 5.—Sagittal section showing a subependymal-plate glioma occupying the posterior and inferior medullary vela and invading the adjacent cerebellar folia (hematoxylin-eosin stain; × 30).

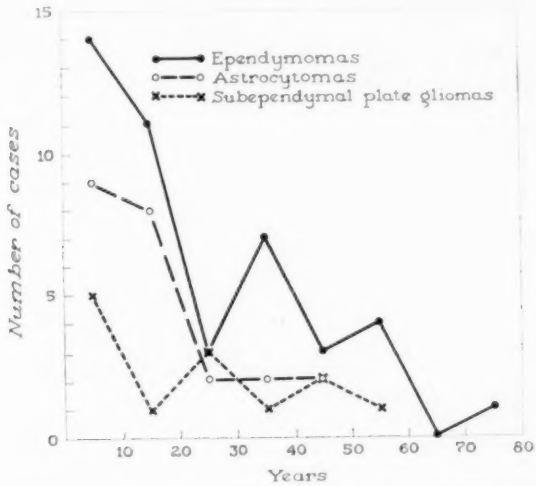


Fig. 6.—Incidence of ependymomas, astrocytomas, and subependymal-plate gliomas of the fourth ventricle according to age of the patients.

Correlation of Predilection of Sites of Origin of Gliomas and Sites of Cell Rests.—The majority of cell rests in the region of the fourth ventricle were either mixed-cell rests or ependymal-cell rests. It would seem possible that a causal relationship between the frequency of occurrence of cell rests of a certain histologic type in certain sites and the frequency with which tumors of the same type arise in that site could be established. For example, ependymomas arise most frequently from the wall of the fourth ventricle posteriorly or from the nodulus; that is, they are predominantly posterior-vermis tumors. The ponticulus, the floor of the fourth ventricle, and the posterior and anterior medullary vela are much less frequently the sites of origin. Ependymal-cell rests, on the other hand, occur most frequently in the ponticulus and the anterior medullary velum. The nodulus and the posterior and inferior medullary vela are much less often the site of ependymal-cell rests. It is obvious that the great majority of ependymomas involving the fourth ventricle do not arise from the structures which abound in ependymal-cell rests. It is difficult to show any causal relationship between the frequency of occurrence of the ependymal-cell rests and the sites of origin of ependymomas. Similarly, it is even more difficult to show such a causal relationship for the other tumors of the glioma group.

TABLE 4.—*Site of Origin of Gliomas of the Fourth Ventricle (Excluding Medulloblastomas)*

Site	Number
Nodulus	29
Wall of the ventricle	26
Floor of the ventricle	13
Anterior medullary velum	7
Ponticulus	4
Posterior medullary velum	3
Total	82*

* Multiple tumors arose from four sites.

Certain observations regarding the frequency of cell rests and the frequency of origin of tumors in specific structures should not be overlooked. Astrocytomas and ependymomas involving the fourth ventricle are predominantly posterior-vermis tumors (Table 4). Thirty-four of a total of 43 ependymomas and 17 of a total of 23 astrocytomas in this study could be considered posterior-vermis tumors. The same region was the site of the majority of cell rests of all kinds. Of a total of 159 cell rests, 105 occurred in the nodulus, the white matter above the fastigium, the posterior medullary velum, or the adjacent ventricular wall. It would appear that there are factors which determine the site of gliomas other than the presence of cell rests of a particular histologic type in a given site.

Six cell rests of the external granular layer were observed in this study. Tumors arising from these rests were not included. It is interesting to note that the tumors described by Stevenson,[12] Stevenson and Echlin,[13] and Scheinker,[14] and classified as medulloblastomas, are considered to arise from cell rests of this type.

12. Stevenson, L.: Tumors of the Cerebellum, Arch. Neurol. & Psychiat. **26**:875-876 (Oct.) 1931.

13. Stevenson, L., and Echlin, F.: Nature and Origin of Some Tumors of the Cerebellum: Medulloblastoma, Arch. Neurol. & Psychiat. **31**:93-109 (Jan.) 1934.

14. Scheinker, I.: Zur Frage der Pathogenese und Pathologie der Medulloblastome, Monatsschr. Psychiat u. Neurol. **101**:103-113 (May) 1939.

In studying the origin of subependymal-plate gliomas, we attempted to correlate the site of tumor predilection with the sites of scattered ependymal cells, spongioblasts, and transitional cells beneath the ependymal lining, as described by Globus and Kuhlenbeck.[15] It was noted in this study that these scattered subependymal elements occurred mostly in the anterior medullary velum and, to a less degree, in the posterior medullary velum. Areas of glial proliferation in the subependymal cell plate occurred most commonly in the same structures.

The most frequent site of origin of the subependymal-plate gliomas was the floor of the fourth ventricle. The nodulus and the anterior and posterior medullary vela were next most frequently involved. It is seen, then, that, as with the other gliomas, the most frequent site which contained rests did not necessarily give rise to the greatest number of tumors.

COMMENT

The problem of the mode of origin of gliomas has been a perplexing one, being but a part of the larger problem dealing with the cause of tumors in general. Although many observations had been made to show that tumor growth in some way was related to the growth of embryonal tissue, it was not until 1882 that Cohnheim[16] first formulated the concept that tumors arose from groups of cells which had retained their embryonal characteristics. These cell rests could be elements dislocated during embryonic development or those which had not been misplaced. This concept was supported by Ribbert,[17] who believed that groups of cells could be isolated even in later life and become the basis of tumors. Although the origin of many gliomas could be explained by this theory, it did not explain the formation of such tumors as astrocytomas. The concept of dedifferentiation, which postulated that the parent cells of the tumor were adult cells and then differentiated back into embryonal cell types, was introduced to account for such tumors. Many other theories have been proposed to explain the origin of tumors, but none has been completely satisfactory.

The concept of a "mosaic of territories," proposed by Lipschutz,[18] perhaps offers a clue to the relationship of cell rests and the origin of tumors. It is considered that the organism is a mosaic of territories and that each territory is independent in its response to a factor which can induce neoplastic growth. The same concept is applied to tissues of homologous cells. In this way, rests of a certain histologic type are not necessarily the locus of a tumor, any more than are other cells of the same type lying in a normal situation. Apparently, it is some intrinsic factor which is present in a cell, or group of cells, that makes the cells susceptible to tumorigenic influences, rather than whether the cells are heterotopic or not.

15. Globus, J. H., and Kuhlenbeck, H.: Tumors of the Striatothalamic and Related Regions: Their Probable Source of Origin and More Common Forms, Arch. Path. **34**:674-734 (Oct.) 1942; footnote 10.

16. Cohnheim, J.: Vorlesungen über allgemeine Pathologie: Ein Handbuch für Ärtze und Studirende, Berlin, A. Hirschwald, 1882, Vol. 1.

17. Ribbert, H.: Neuroepithel in Gliomen, Zentralbl. allg. Path. **21**:145-148 (Feb.) 1910; Über das Spongioblastom und das Gliom, Virchows Arch. path. Anat. **225**:195-213 (Aug.) 1918.

18. Lipschutz, A.: Steroid Hormones and Tumors: Tumorigenic and Antitumorigenic Actions of Steroid Hormones and the Steroid Homeostasis: Experimental Aspects, Baltimore, Williams & Wilkins Company, 1950.

Another concept which aids in an understanding of the possible mechanisms responsible for tumor growth in the region of the fourth ventricle is one which has been advanced by experimental embryologists, that is, the concept of morphogenetic fields.[19] It is known that certain embryonal tissues possess some mechanism, chemical or otherwise, whereby the relative growth of different parts of a certain region and the differentiation of special cell types in that region are controlled. From a developmental point of view, it is evident that the posterior rhombic lip of the cerebellum, especially the central nodular portion, must be such a center controlling the relative growth of the component parts of the cerebellum and its cellular differentiation. This region is the most primitive part of the cerebellum, and through the proliferation of bipotential cells from the germinal bud it supplies many neuronal and glial elements. In mammals the effect of the morphogenetic field is presumed to become weaker in later life, acting over relatively short distances and being confined to the control of minor repair growth in the body.[19c]

The relationship of the induction of embryonic structures to their morphogenetic activity and malignant growth has been discussed by Needham,[19d] Berrill, Lehmann, Holtfreter,[19b] Briggs,[19a] and others. Many investigators believe that it is some intrinsic property of a cell or group of cells which causes them to become refractory to the normal growth-controlling mechanisms and to become autonomously growing cancer cells. Although normal and malignant cells differ in such characteristics as chromosomal behavior, rate of cell division, chemical composition, and metabolism, it is not known which is the most important in determining malignancy.

It is only by thinking in terms of these concepts that the origin of gliomas of the fourth ventricle can be better understood. The results of this study show that cell rests of a particular histologic type occurring frequently in a certain structure do not necessarily give rise to tumors of that histologic variety most frequently in that structure; instead, the nodular region of the cerebellum is implicated as being the most frequent site of gliomas other than medulloblastomas. Whether the indifferent, bipotential germinal cells found in the mixed-cell rests in the nodular region are the parent cells of several kinds of glioma cannot be stated with certainty.

SUMMARY

This report is based on a study of 79 cases of glioma of the fourth ventricle. Of the 79 gliomas, 43 were ependymomas, 23 were astrocytomas, and 13 were subependymal-plate gliomas.

In the cases of ependymoma, the posterior part of the wall of the fourth ventricle and the nodulus were assigned most frequently as the probable sites of origin. The

19. (*a*) Briggs, R.: Embryology and Cancer, Clinics **4**:112-117 (June) 1945. (*b*) Holtfreter, J.: Concepts on the Mechanism of Embryonic Induction and Its Relation to Parthenogenesis and Malignancy, in Symposia of the Society for Experimental Biology No. II: Growth in Relation to Differentiation and Morphogenesis, London, Cambridge University Press, 1948, pp. 47-49. (*c*) Waddington, C. H.: Cancer and the Theory of Organisers, Nature, London **135**:606-608 (April 20) 1935. (*d*) Needham, J.: Biochemistry and Morphogenesis, London, Cambridge University Press, 1942.

nodulus was the site of origin assigned most frequently to astrocytomas involving the fourth ventricle. Subependymal-plate gliomas arose most frequently from the floor of the fourth ventricle. In one case multiple sites of origin were observed.

In the cases of these three types of glioma, most of the patients were males.

In most of the cases of ependymoma and astrocytoma, the tumor occurred in the first two decades of life. A more even distribution in the age groups was observed in cases of subependymal-plate gliomas.

No correlation was noted between the frequency of cell rests of a certain histologic type occurring in a specific structure and the frequency of tumors of the same histologic type arising in that structure. The region of the nodulus in the posterior vermis was the most frequent site of origin of the gliomas in this study. This region was also the most frequent site of mixed-cell rests.

STUDIES ON ANXIETY ASSOCIATED WITH ANTICIPATION OF PAIN

I. Effects of Morphine

HARRIS E. HILL, Ph.D.

CONAN H. KORNETSKY, M.S.

HAROLD G. FLANARY, M.S.

AND

ABRAHAM WIKLER, M.D.

LEXINGTON, KY.

AS WOLFF, HARDY, AND GOODELL [1] have emphasized, the potent analgesic agents, such as those of the opiate group, appear to exert their most striking effects on reactions to pain. However, the evidence available indicates that such reactions to pain as the change in skin resistance and head withdrawal are not closely related to the pain experience (Wikler [2]). Thus, Isbell [3] has shown that small doses of barbiturates may reduce markedly the change in skin resistance which follows radiant-heat stimulation. Chapman, Rose, and Solomon [4] have demonstrated that after frontal lobotomy pain is relieved and yet head-withdrawal responses to radiant-heat stimuli may actually become enhanced.

However, a number of observations suggest the possibility that the anticipation of pain is an important component of the pain experience and that the primary action of potent analgesic agents is exerted upon this particular "reaction to pain."

That anticipation of pain is an important component of the pain experience is common knowledge and has been demonstrated repeatedly. Thus, Mowrer and Viek,[5] Estes and Skinner,[6] and others have shown that a stimulus which precedes a noxious stimulus shortly acquires the function of producing anticipatory fear

From the National Institute of Mental Health, Addiction Research Center, United States Public Health Service Hospital.

1. Wolff, H. G.; Hardy, J. D., and Goodell, H.: Studies on Pain: Measurement of the Effects of Morphine, Codeine, and Other Opiates on the Pain Threshold and on Analysis of Their Relation to the Pain Experience, J. Clin. Invest. **19**:659-680, 1940.

2. Wikler, A.: Sites and Mechanisms of Action of Morphine and Related Drugs in the Central Nervous System, Pharmacol. Rev. **2**:435-506, 1950.

3. Isbell, H.: Unpublished data.

4. Chapman, W. P.; Rose, A. S., and Solomon, H. C.: Measurements of Heat Stimulus Producing Motor Withdrawal Reaction in Patients Following Frontal Lobotomy, A. Res. Nerv. & Ment. Dis., Proc. **27**:754-768, 1948.

5. Mowrer, O. H., and Viek, P.: An Experimental Analogue of Fear from a Sense of Helplessness, J. Abnorm. & Social Psychol. **43**:193-200, 1948.

6. Estes, W. K., and Skinner, B. F.: Some Quantitative Properties of Anxiety, J. Exper. Psychol. **29**:390-400, 1941.

reactions. Estes and Skinner have shown that under these conditions the "conditioned" noxious stimulus produces more disruption of behavior than the "unconditioned" noxious stimulus. On the other hand, anticipation of pain may be modified considerably by cultural factors. For instance, Moloney [7] showed that very young Okinawan children exhibit anticipatory fear of pain to a degree that is comparable to that among Occidentals. However, older children exhibited the characteristics of the "typical" Oriental in displaying very little fear of pain. Similarly, it has been observed that Chinese patients who have been reared in Oriental cultures exhibit little anticipatory fear of the withdrawal procedure during treatment for narcotic addiction, whereas Americans of Chinese descent react much like Occidentals (Isbell [8]). It would be pertinent to the hypothesis concerning the relation of anticipatory anxiety to the pain experience to determine whether Orientals actually suffer less than Occidentals under similar experimental conditions involving pain.

That measures which relieve pain also reduce the anticipation of pain is indicated by a number of observations. Thus, Malmo and Shagass [9] showed that frontal lobotomy reduces to a striking degree such motor responses as are anticipatory of painful stimuli, in contrast to the effect of this procedure on direct responses to painful stimuli (Chapman, Rose, and Solomon [4]). There is clear evidence, also, that morphine reduces anticipation of pain. Thus, in a previous report, it was demonstrated that experimental conditions which are conducive to the enhancement of anxiety (fear of pain) also promote overestimation of the intensities of painful stimuli.[10] In analgesic doses (15 mg.) morphine sulfate reduced or abolished this error but had no significant effect on the ability to estimate intensities of painful stimuli when experimental conditions were such that anxiety was largely dissipated. That study provided objective evidence on the influence which anxiety and morphine exert on one aspect of the subjective pain experience. However, it appeared to be desirable from a heuristic standpoint to develop a method which would provide measurements that were independent of the subject's report. Therefore, the present problem is concerned with testing the effects of anxiety and of morphine, and of the two combined, upon a simple "overt performance."

The hypothesis that underlay the planning of the investigation was as follows: Efficiency of performance, such as is measured by recording reaction times to visual stimuli, is dependent upon motivation, i. e., particular experimental conditions. When motivation is optimal, minimal reaction times can be expected; when motivation is low, longer reaction times may be expected, and when motivation is excessive, a disruption of performance may be expected, as indicated by long and variable reaction times.

Thus, if fear of pain is utilized as the motivating condition, large variations in visual reaction times may be expected when avoidance of the painful stimulus

7. Moloney, J. C.: The Magic Cloak, Wakefield, Mass., Montrose Press, 1949, p. 299.

8. Isbell, H.: Unpublished data.

9. Malmo, R. B., and Shagass, C.: Behavioral and Psychological Changes Under Stress After Operations on Frontal Lobes, Arch. Neurol. & Psychiat. **63**:113-124 (Jan.) 1950.

10. Hill, H. E.; Kornetsky, C. H.; Flanary, H. G., and Wikler, A.: Effects of Anxiety and Morphine on the Discrimination of Painful Stimuli, Federation Proc. **10**:309, 1951.

becomes increasingly difficult. Furthermore, if morphine, as hypothesized, reduces anticipation of pain, its administration should eliminate to a significant degree the disrupting effects that are due to the anticipation of painful stimuli.

METHODS AND MATERIAL

Subjects.—Fifty-eight former addicts (patients with previous histories of narcotic addiction) and four staff physicians were used in the exploratory and final studies. The statistical data are presented on 22 former addicts who served on the final study and on the mixed group of 8 subjects who were among the first subjects tested. Because of its severity, two personnel members and three former addicts withdrew from the test. Significantly, all such withdrawals from the test occurred only on days when morphine had not been administered. The remainder of the subjects were used for exploratory purposes or were disqualified because of technical or procedural difficulties.[11]

Apparatus and Procedure.—A considerably modified form of the traditional reaction-time apparatus was employed; the differences lay mainly in the number and order of presentation of stimuli and in the use of additional electric shocking devices.

Bipolar, flat stainless steel electrodes covered with saline paste were attached to the reacting hand of the subject for all tests, and when electric stimuli were used, a commercial inductorium generated shocks of approximately 140 volts and 0.37-second duration. Hand reaction times, in milliseconds, were recorded by a modified Dunlap chronoscope when the subject pressed a key in response to the flash of a neon bulb. The response key and four neon bulbs were mounted on an opaque screen, 4½, 10, 15, 16, and 17 in. (1.9, 25.5, 38, 40.5, and 43 cm.), respectively, above a table, in vertical alignment. For instructional purposes, the subject was told that the bulbs would be lit in an "on your mark," "get set," "go" sequence. The lowest light indicated that a trial was beginning. The second bulb from the top flashed two seconds later and indicated that the subject should prepare for a quick response. The other two lights, one slightly above and one slightly below the "get set" bulb, were the stimulus lights. Only one of these was lit for any one trial, the subject responding to either by quickly moving the key to the left. The delay time, or foreperiod, between the warning and stimulus lights was variable, a predetermined random order of 1, 2, or 3 seconds being used.

Two practice sessions of 18 reactions each were given 15 minutes apart to all subjects for all conditions. If scheduled, medication was then administered, and a 45-minute period was allowed to elapse before the tests were resumed. Six experimental series of 18 reactions each, separated by 15-minute intervals, were then obtained. Each subject spent four half-days, extending over a two-week period, on the following four conditions: (1) shock penalties for relatively slow reactions, (2) shock penalties for relatively slow reactions after morphine medication, (3) control, (4) morphine medication. Conditions 1 and 2, and 3 and 4 were given in balanced order, which was designed to obviate serial effect; and, except for the administration of morphine, the balanced conditions were equivalent, shock being used only during the first two conditions.

For the practice sessions, the two stimulus lights had identical meanings for the subjects: "Press the key as quickly as possible." The procedure for control and morphine medication days (Conditions 3 and 4) on the test series was as follows: After the 45-minute interval the subject returned and was told that the following series would start with the flash of the third light from the top, and that if his movements were sufficiently quick this light would be used as the signal for all following reactions. However, it was indicated that slow reactions would be followed on the next trial by the top light; in this way, the subject would be given knowledge of his performance and thus be motivated to perform more quickly. For Conditions 1 and 2,

11. Twenty-eight subjects were disqualified, for the following reasons: Two personnel men and 3 former addicts withdrew from the test; 1 former addict became ill; the protocols of 4 former addicts were discarded because of difficulties with the apparatus; 6 former addicts were used in an exploratory choice-reaction-time study; 12 former addicts were employed for initial exploratory work.

in which shock was used, the subject was given the above instructions; in addition, he was told that the upper light would mean that a strong shock would be delivered just as he completed the pressing of the key. In this way, the subject was forced to penalize himself just as his responses were terminated.[12]

The subject's practice mean was taken as the criterion for applying the upper light for the first test series. As each series was completed, median reaction times were calculated. If improvement had occurred, a new criterion, the lowest median value, was established. Thus, the new criterion was lowered to a point at which 9 of 18 reactions to the upper light would occur if the subject maintained his efficiency. Nevertheless, the criterion was not shifted upward when less efficient behavior began to occur but was maintained at the lowest point. As indicated previously, during shock days the upper light was followed by a strong shock as the subject completed the movement of the key.

Treatment of Data.—Mean reaction times were obtained for each subject, and these were combined to give a group means for the practice periods and means for each of the six experimental series. The differences between the means of the six series for Conditions 1 and 2 and the means for Conditions 3 and 4 were evaluated by the t test, using the difference method (Edwards [13]). Emphasis was placed on the outcome for a group of 16 subjects whose performance deteriorated under shock conditions. The performance of 6 of the 22 subjects was not disrupted by repeated shock penalties, any measurable effect of morphine being thereby precluded.[14] The group of 16 subjects were composed of those persons whose actual reaction times under conditions of shock without morphine exceeded their practice mean after 0.016 second was deducted from the latter. This figure was calculated to be the average decrease in reaction time which could be expected to occur after one day as the result of learning.

The results for this group were subjected to the t test for evaluation of the differences between shock and shock-morphine conditions and between control and morphine conditions. Since the scatter of scores, or the variability of behavior, has been used frequently as a significant indicator of emotional disruption of behavior, a comparison was made also of the standard deviations of the shock and shock-morphine conditions. Graphic treatments are presented also of the results obtained on eight subjects used in preliminary experiments who received less intense shock stimuli than were used for the main group.

RESULTS

Although measurements on the entire group of 22 subjects were not used in the final calculation for determining the effects of morphine on anticipatory

12. Several factors which have been found to contribute to the production of "experimental neurosis" are seen to have been incorporated in this situation: (1) The subject was constrained to produce a specific response; (2) the demanded response might be severely punished; (3) the subject was forced to penalize himself; (4) the response was penalized immediately upon its completion; (5) the periods between stimulations, and between the warning and the stimulus light, presented an opportunity for unfavorable anticipatory responses, since the subject never knew which of the two lights was going to appear next.

13. Edwards, A.: Statistical Analysis for Students in Psychology and Education, New York, Rinehart & Co., Inc., 1946, p. 174.

14. As reported in a separate paper (Hill, H. E.; Flanary, H. G.; Kornetsky, C. H., and Wikler, A.: Relationship of Electrically Induced Pain to the Amperage and the Wattage of Shock Stimuli, to be published), subjects judge the intensity of electrical stimuli on the basis of wattage, and not on the basis of voltage or amperage. Thus, part of the reason that 6 of the 22 subjects did not exhibit disruption of behavior may have been that equal voltages were applied to all subjects; a subject whose skin resistance was high would not receive as great a power as one whose skin resistance was low. On the other hand, the efficiency of subjects who did not exhibit deterioration of reaction times under shock may have been due to personality factors. Probably the reason that deterioration did not occur in all subjects was that a low power of stimulation and personality factors functioned singly or in combination.

responses, these data are presented graphically in Chart 1.[15] When shock was not administered, 15 mg. of morphine sulfate increased the reaction time significantly. The *t* value was 2.82, which indicates a probability of chance occurrence of slightly more than the 1% level. When shock was administered on days when morphine was not given, the reaction time became progressively slower. Under shock conditions after administration of morphine, such slowing of the reaction time, due to

TABLE 1.—*Mean Reaction Times, in Seconds, Under Four Conditions* for Sixteen Subjects*

Condition	Practice	Test Series					
		1	2	3	4	5	6
Shock	0.249	0.272	0.275	0.281	0.286	0.279	0.289
Shock and morphine sulfate	0.256	0.257	0.257	0.254	0.257	0.261	0.283
Control	0.234	0.222	0.230	0.230	0.229	0.230	0.228
Morphine sulfate	0.237	0.228	0.233	0.238	0.238	0.239	0.241

* The first two conditions and the last two were given in separate balanced order. Balancing the first two and the last two conditions did not result in equal practice means because six subjects were excluded from the final calculations. The practice means for the entire group were as follows: shock, 0.258; shock and morphine, 0.258; control, 0.235; morphine, 0.237.

TABLE 2.—*Series Mean Reaction Times, in Seconds, for Shock and Shock-Morphine, with Differences, Standard Errors of Differences, t's, and P's for Sixteen Subjects*

Series	Shock	Shock and Morphine Sulfate	Difference	σ Means Difference	*t*	*P**
1	0.272	0.257	0.015	0.012	1.25	>20
2	0.275	0.257	0.018	0.014	1.29	>20
3	0.281	0.254	0.027	0.011	2.45	< 5
4	0.286	0.257	0.029	0.010	2.90	< 2
5	0.279	0.261	0.018	0.014	1.29	>20
6	0.289	0.283	0.006	0.022	0.27	>20

* The *P* column indicates the probability that these results would occur by chance in 100 repetitions.

TABLE 3.—*Standard Deviations (Seconds), Differences, Standard Error of Differences, t's and P's for Sixteen Subjects*

Series	Shock	Shock and Morphine	Difference	σ Means Difference	*t*	*P*
1	0.0589	0.0503	0.0086	0.0101	0.85	>20
2	0.0720	0.0599	0.0121	0.0130	0.93	>20
3	0.0982	0.0544	0.0138	0.0059	2.34	< 5
4	0.0936	0.0455	0.0241	0.0084	2.87	< 2
5	0.0772	0.0501	0.0271	0.0112	2.42	< 5
6	0.0889	0.0938	0.0049	0.0180	0.27	>20

previous shock penalties, was strikingly reduced up to the fifth series (two hours after injection of morphine).

The data for the 16 subjects are summarized in Tables 1, 2, and 3 and are shown graphically in Chart 2. It will be noted that absolute values are given in Table 1

15. Because of the interdependence of the subject's responses and the heterogeneous slopes of the curves, no statistical method is known to us by which the *t*'s can be combined for all series under any of the four conditions used in the experiment. Therefore, because none of the individual *t*'s for the entire group was statistically significant, the data on the group of 22 subjects will be presented in graphic form only.

and that the calculations indicated in Tables 2 and 3 are based upon these values, whereas an equalization process was performed for ease of graphic presentation. Table 2 and Chart 2 show, by series, a comparison of reaction times obtained under shock conditions with those obtained under shock after the administration of

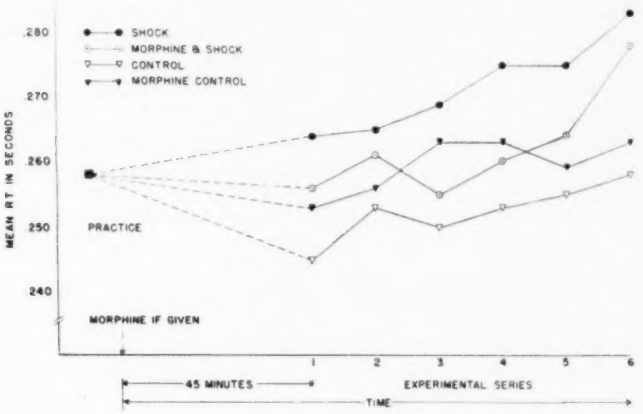


Chart 1.—Reaction time under various conditions for the entire group of 22 subjects.

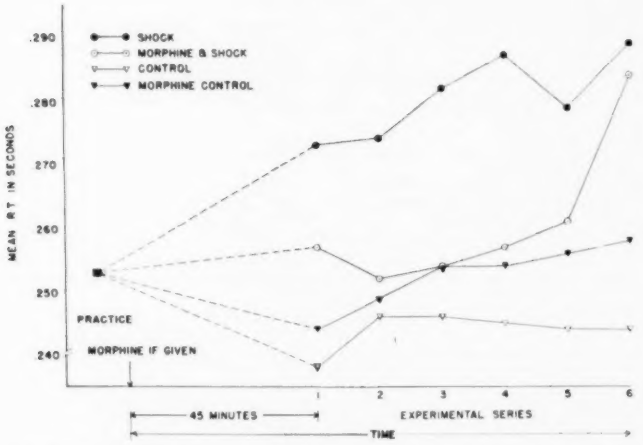


Chart 2.—Reaction time under various conditions for the group of 16 subjects.

morphine. The two curves diverge markedly, the difference at Series 3 being significant beyond the 3% level and that for Series 4 beyond the 2% level. Table 3 indicates that very similar results occurred in the variability of scores; for Series 3 and 4, scatter, as shown by the standard deviation, is significantly reduced by

morphine at probability levels that are comparable to those found between the means.

It can be observed in the tables that control conditions resulted in the shortest reaction times, followed by the morphine condition, the shock-morphine condition, and the shock condition alone, in that order of increasing reaction times. An even more striking outcome occurred in a preliminary group of eight subjects. Results obtained from these subjects are shown in Chart 3. The curves for the control and morphine groups are very similar to those found for the other groups. The curve for the shock group is maintained at approximately the practice level through Series 4, and considerable disruption is indicated at Series 5 and 6. However, a strikingly different curve was obtained for reaction times under shock after the administration of morphine. Consistently shorter times were recorded for this entire test period than for any other condition.

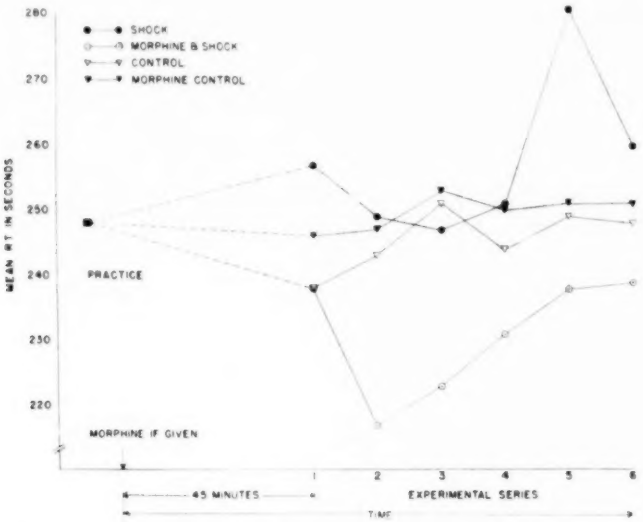


Chart 3.—Reaction time under various conditions for the group of eight preliminary subjects.

COMMENT

One of the primary purposes of the study was the production of short-term disruption of behavior due to anticipation of noxious stimuli; attainment of this objective was necessary for measuring the effects of morphine. There is no doubt that this disruption of behavior was accomplished in 16 of 22 subjects. Reaction times for all pilot and experimental groups were consistently greater under shock than under control conditions. In addition, at the time the five subjects referred to above withdrew from the test, their reaction times were considerably greater than the mean shock-reaction times, showing that some of the most indicative data could not be included in the results. That the disturbance which occurred was consequent to the anticipation of the shock can be logically deduced from the

experimental design and from the spontaneous reports of the subjects. Nearly all subjects stated that it was not so much the shock that disturbed them as it was the expectancy, the uncertainty of the stimulation.

The administration of morphine produced several different effects, depending upon the particular experimental conditions. When shock was not a part of the procedure, morphine resulted in a small but significant increase in reaction time. When shock penalties were employed, the predictable slowing of reaction time was significantly reduced by morphine in the shock-sensitive group. When such shock penalties were mild, morphine actually reduced reaction times to levels that were the shortest recorded under any of the conditions utilized in these experiments.

It can be seen that morphine protected the susceptible subjects from the deleterious effects of shock for the first 90 minutes of the test. Morphine also produced an increase in efficiency in this simple type of response when motivation was high, but not sufficiently high to be disrupting. These actions cannot be attributed to impairment of the ability to estimate the intensity of painful stimuli, since it had previously been shown that after the administration of morphine a subject's ability to compare stimulus intensities with a previously given standard is actually improved.[1] Therefore, it may be concluded reasonably that morphine reduces the disruptive effects on performance that are associated with the anticipation of pain. Although the procedure of the present experiment, in which anxiety was deliberately produced, was the reverse of that employed in the previous study,[1] the outcomes were very similar. The results of both were consistent with the hypothesis that morphine alleviates or reduces the disruptive effects on performance that are associated with the anticipation of pain. However, the data thus far obtained do not prove conclusively that reduction of fear of pain and the relief of pain by morphine are entirely commensurable. More support for such a correlation would be afforded by the demonstration that all the potent analgesics have actions which are similar to those described in the present report for morphine, and, also, that nonanalgesic drugs do not exert such effects. Such studies are now in progress.

SUMMARY AND CONCLUSIONS

In former addicts, hand reaction times to visual stimuli on days without morphine were compared with those after subcutaneous injection of 15 mg. of morphine sulfate under the following conditions: (*a*) The subjects were motivated only by a general knowledge of their performance, and (*b*) the subjects were penalized by a self-administered brief, but strong, electric shock to one hand immediately after each response, which was slower than the shortest previous median value.

The shortest reaction times occurred in nonmorphinized subjects who were not penalized for long reaction times. Morphine alone increased reaction times significantly. Electric-shock penalties to nonmorphinized subjects also increased reaction times significantly.

When electric-shock penalties were delivered to morphinized subjects, reaction times were not increased above the level effected by morphine alone during the first 1½ hours after injection of the drug; indeed, in some subjects, reaction times under these conditions were shorter than any of the others.

It is concluded that morphine reduces the disruptive effects on performance which are associated with anxiety produced by anticipation of pain.

COMBINED USE OF ETHYL ALCOHOL AND AMOBARBITAL (AMYTAL®) SODIUM FOR AMBULATORY NARCOANALYSIS

MICHAEL M. MILLER, M.D.
WASHINGTON, D. C.

ONE OF the principal problems encountered in employing drugs such as amobarbital (amytal®) sodium or thiopental (pentothal®) sodium for ambulatory narcoanalysis is that patients may sometimes become immobilized for several hours or longer, owing to the hypnotic action of the drug. This, obviously, makes it hazardous to release such patients from the clinic prior to recovery from the effects of the drug. Another problem is that of administering the optimum dose so as to obtain a satisfactory twilight narcosis and not to induce sleep. Much valuable clinic time is often spent in attempting to revive patients in whom deep sleep has been induced. In order to avoid overdosage and to maintain the proper level of therapeutic narcosis it has been necessary to inject these drugs very slowly and to repeat the injection. In addition, tolerance to barbiturates may vary considerably. Even with the barbiturates above mentioned, the differences in the amounts required for inducing therapeutic narcosis as compared with those required for sleep are relatively small, making proper dosage difficult.

The problem, obviously, was to seek out and study a suitable drug which, in appropriate doses, would have a briefer period of action and a minimum sleep-producing effect and still would have a pronounced action in blocking the psychic inhibitory mechanisms and in releasing emotionally charged memories, conflicts, and fantasies. Ethyl alcohol appeared to be such a drug. An attempt was made to evaluate its effectiveness in narcoanalysis and then to study the combined administration of one of the commonly employed barbiturates and alcohol.

Since ancient times, it has been more or less common knowledge that "wine loosens the tongue," or, as the Romans put it, "*in vino veritas*" ("truth is in the wine"). Undoubtedly, the ancients had a considerable awareness of the psychic effects of alcohol and drank to relieve their troubled spirits. A great poet of the Elizabethan era was said to have lamented: "It increaseth the desire but lesseneth the performance," indicating the action of alcohol in releasing repressed sex urges.

Of interest was Abraham's[1] observations on the effects of alcohol in releasing repressed desires when he pointed to the fact that alcohol could relieve inhibitions sufficiently to disclose a latent homosexuality in so-called normal persons.

More recently, Newman's studies at Stanford University on the effects of alcohol on psychoneurotic and psychotic patients has contributed additional excellent data in evaluating its use as a therapeutic agent.

From Howard University College of Medicine, Division of Neuropsychiatry.

1. Abraham, K.: Ztschr. Sexualwissensch., 1908, p. 449.

PHARMACOLOGICAL CONSIDERATIONS

In preliminary tests, it was noted that although the action of ethyl alcohol administered intravenously in moderate doses (4 to 6 cc. of absolute alcohol in 15 to 20% solutions) was rather generalized on areas of the psyche and personality, nevertheless, it was apparent that two areas of function were most affected; that is, the exercise of morale censorship and social inhibition appeared markedly diminished (blocking of repressive functions of conscience—superego), and repression of speech was lifted, resulting in loquacity and generally increased speech productivity. This view appears to be confirmed by the much earlier observations of Schmiedeberg,[2] who pointed out that alcohol weakens the highest functions of the brain—the will and self-restraint—and that the drug tends, even in small quantities, to act most strongly on the most recently acquired faculties of self-control and sense of responsibility. The aforementioned action facilitates the release of both consciously suppressed and unconsciously repressed conflictual material and fantasies. It was further observed that considerable quantities of ethyl alcohol could be tolerated by most patients without producing sleep. Tolerance to alcohol was found to be an important factor and undoubtedly accounted for considerable differences in the response to the drug. Newman observed that alcohol produced greater communicability, loquaciousness, and rapport in neurotic patients.

Mellanby [3] found that alcohol was consumed at a fairly constant rate in the body at the equivalent of 10 cc. per hour of a 95% solution of absolute alcohol. Thus, it is clear that 4 to 6 cc. of absolute alcohol administered in diluted solution should be oxidized in approximately 30 to 40 minutes. However, it was not found very convenient to inject larger quantities of dilute (15%) alcohol intravenously, and, as aforementioned, the range of tolerance sometimes varied considerably. These facts led to the question as to whether a more effective result could be achieved with relatively small doses by exploiting the synergistic action of alcohol and barbiturates (Olszycka,[4] Dille and Ahlquist,[5] Dille and Koppanyi [6]).

Although Olszycka [4] found that simultaneous administration of ethyl alcohol and ethylbutylbarbituric acid to rats produced a marked potentiation of sleep effect, Allegri and Carrière,[7] and Carrière, Huriez, and Willoquet [8] observed that alcohol retarded onset of sleep in rabbits given phenobarbital, shortened sleeping time, and protected the animals from a lethal dose of this barbiturate. These results appear contradictory; however, there are factors which may account in part for the discrepancy. Olszycka administered the alcohol and barbiturate simultaneously, and it is of interest that Dille, Koppanyi, and associates found in studies on dogs that greater and more rapid concentrations of barbiturate in the brain occur if barbiturates are administered simultaneously with 50% ethyl alcohol. This synergism of alcohol and barbiturates, I believe, rests very likely on the fact that alcohol has a

2. Schmiedeberg, O., cited in Cushny's Pharmacology and Therapeutics, edited by C. W. Edmunds and J. A. Gunn, Philadelphia, Lea & Febiger, 1940, p. 291.

3. Mellanby, E.: Medical Research Council, Special Reports, London, His Majesty's Stationery Office, 1919.

4. Olszycka, L.: Compt. rend. Soc. biol. **201**:795, 1935; ibid. **202**:1107, 1936.

5. Dille, J. M., and Ahlquist, R. P.: J. Pharmacol. & Exper. Therap. **61**:385, 1937.

6. Dille, J. M., and Koppanyi, T.: J. Pharmacol. & Exper. Therap. **52**:91, 1934.

7. Allegri, A., and Carrière, G.: Boll. Soc. ital. biol. sper. **10**:48, 1934.

8. Carrière, G.; Huriez, C., and Willoquet, P.: Comp. rend. Soc. biol. **116**:188, 1934.

considerably higher degree of solubility in lipids and acts as a vehicle for barbiturates, carrying considerably more barbiturate into the brain. Aqueous solutions are far less soluble in lipids and hence penetrate the brain more slowly and to a slighter degree (Meyer-Overton[9] theory of narcosis).

The ideal drug effect sought for narcoanalysis is, of course, one which blocks the repressive functions sufficiently to permit release of affect-laden conflictual experiences and fantasies which have been repressed without seriously disturbing the flow of ideas, recollections, and speech productivity. Although such barbiturates as amobarbital sodium and thiopental sodium act to block the repressive functions, these drugs also produce a general diminution of cerebration, with a corresponding reduction in verbal productivity and the flow of ideas. Patients become less communicative, and active questioning must usually be pursued. As aforementioned, alcohol greatly steps up communicativeness and speech productivity. Although alcohol in larger amounts produces dissociation of thought and affect, there is little or no observable dissociation with small quantities, such as was employed in the present study.

It is certainly untrue that alcohol improves memory or any associational functions; nevertheless, the release of repressed memories may be effected by these drugs, and it is just this repressed material that is of the greatest value to the therapist.

It was found that the blood alcohol level could rapidly be raised to the desired concentration when the alcohol was administered by the intravenous route, whereas a considerable quantity of alcohol is required for an equivalent blood level when given by the oral route.

There has been considerable controversy over the question whether moderate amounts of alcohol stimulate respiration. Most authorities agree that alcohol in moderate doses increases the depth of respiration and has a general stimulating action on the blood pressure and pulse. Alcohol eases the work of the heart, owing to its vasodilating action on surface vessels. It also has a beneficial dilating action on the coronary vessels. On the other hand, barbiturates are strong respiratory-circulatory depressants. Quastel and associates[10] found that in barbiturate narcosis there is an inhibitory effect of barbiturates on glucose oxidation in the brain tissues. Alcohol appears to oxidize rapidly and increases oxygen consumption of the brain. Alcohol, like amphetamine sulfate, greatly increases oxygen consumption in the brain, tending in smaller amounts, such as were employed in this study, to produce euphoria and a sense of well-being, rather than the depression of mood resulting from barbiturates. In addition, alcohol counteracts certain undesirable side-effects of barbiturates, such as excitement, fear, maniacal delirious reactions, and extreme depression.

TECHNIQUE OF ADMINISTRATION

Amobarbital sodium, 2 to 3¾ grains (120 to 230 mg.) in 20 to 25 cc. of a 10 to 15% solution of ethyl alcohol (in isotonic sodium chloride) was given intravenously, the dose being adjusted approximately to the patient's body weight. For instance, a patient of 120 lb. (54.4 kg.) would

9. Meyer, H. H.: Arch. exper. Path. u. Pharmakol. **42**:109; **46**:338, 1899. Overton E.: Studien über die Narkose, Jena, C. Fischer, 1901.

10. Quastel, J. H., and Wheatley, A. H. M.: Proc Roy. Soc., London, s.B **112**:60, 1932. Quastel, J. H.: Physiol. Rev. **19**:135, 1939.

receive 2 grains of amobarbital sodium. This concentration of alcohol rapidly becomes isotonic in the blood stream if injected slowly. We found it advisable to use a large-size hypodermic needle, for the following reasons:

1. A slower rate of injection is insured, so that the reaction of the patient can be better observed. The average injection time was two to four minutes.

2. Too rapid injection of alcohol solutions of such concentration often causes pain radiating from the site of injection to the shoulder.

3. It is less traumatic and easier to enter the vein with a large-size needle.

RESULTS

Alcohol-amobarbital sodium narcoanalysis was attempted experimentally in 50 patients with nervous disorders. Of these, 48 had disturbances diagnosed as psychoneurosis in which psychic trauma, in the greater number, played a significant etiological role. Two of the group were classed as schizoid personalities with probable early schizophrenic manifestations in which some disassociation had developed.

Comparative Effects on Verbal Productivity, Emotional Discharge, Dissipation of Drowsiness, and Gross Clinical Ataxia of Amobarbital Sodium Alone and Combined with Ethyl Alcohol *

	Average Duration of Intravenous Effect, Min.		
	Amobarbital Sodium, 3¾ Grains	Amobarbital Sodium, 3¾ Grains, and Alcohol (15%), 25 Cc.	Amobarbital Sodium, 2 Grains and Alcohol (15%), 25 Cc.
Verbal productivity; emotional discharge	90	109	49
Dissipation of drowsiness	93	117	55
Ataxia (gross clinical)	86	109	37

* Twelve female controls were employed, and comparative doses were administered to each at interval periods of 48 hours or longer.

In a high percentage of our patients, 20 to 25 cc. of a 15% alcohol solution and 2 to 3¾ grains of amobarbital sodium, given simultaneously by intravenous injection yielded excellent results as regards increasing verbal productivity, general communicativeness, rapport, and lifting of the psychic repressive functions. Optimum results in most patients studied were obtained with the smaller doses.[11] Clinically, satisfactory narcoanalytic interviews were obtained in all but three patients. Verbal productivity was increased in all but two of the 50 patients observed. Rapport was favorably affected in 48 patients. Euphoria was observed in 40 patients. Excessive narcosis (sleep) was induced in only one patient.

The amounts of barbiturate required were greatly reduced as a result of the potentiating action of the combined drugs. There appeared to be a more rapid dissipation of the psychic and motor effects of the alcohol-barbiturate given.

In contrast to amobarbital sodium or thiopental sodium, the combined alcohol-amobarbital sodium solution given intravenously did not appear to depress circulation or respiration, and in most patients it appeared initially to stimulate blood pressure, pulse volume, and pulse rate and to deepen respiration, although often slowing

11. Optimum results were obtained with 1½ to 2½ grains (90 to 150 mg.) of thiopental sodium administered in 20 to 25 cc. of 10 to 15% ethyl alcohol solution, the amount varying with the patient's body weight.

the respiration rate slightly. The recovery of conscious awareness and sufficient orientation occurred sooner than in patients who had been given amobarbital sodium alone in the doses required for narcoanalysis—3¾ to 7½ grains (230 to 450 mg.) in the average patient. Likewise the recovery of motor coordination and mobility occurred more rapidly than with amobarbital or thiopental sodium alone largely owing to the smaller amount of barbiturate required. The patient could therefore be released from the clinic sooner to resume his particular activity without hazard. The subjective response to the combined drugs was very favorable, in particular as regards mood. It was believed that the cathartic effect of the interviews was greater than with either amobarbital or thiopental alone.

A more accurate control of the degree of narcosis was effected. In contrast to our experience with amobarbital sodium alone, of significance is the observation that when the interview was conducted before students or physicians for teaching purposes, there was little difficulty in maintaining rapport, and resistance was minimal or absent with the combined alcohol-amobarbital method.

It has been my opinion for some time that the synergism, as well as certain antagonistic actions, of alcohol and barbiturates is of great therapeutic significance. This synergism and potentiation of action can be best explained by applying the Meyer-Overton theory of narcosis. Barbiturates in an alcoholic vehicle can be much more effective than when administered in an aqueous solution, even when relatively smaller doses are employed. In addition, barbiturates are more soluble and better maintained in solution in dilute ethyl alcohol than in aqueous solutions. Alcohol, in the moderate doses employed in this study, counters the depressant action of barbiturates on respiration and circulation. The rapid cerebral penetration of these drugs in combination raises the question of the value of such administration in anesthesia. In addition, the possibility of using smaller doses of thiopental, for example, diminishes the danger of undesirable side-effects, such as respiratory paralysis and excessive decrease in blood pressure. This modified administration should be attempted in oral, as well as in intravenous anesthesia.

Members of the Department of Obstetrics and Gynecology, and the Department of Anesthesiology (Dr. C. B. Le Compte, Director), Howard University College of Medicine, under Prof. Julian W. Ross, M.D., are now collaborating on this problem, and further data will be released as soon as adequate investigation is completed.

Mrs. Rose C. Thomas, psychiatric social case worker, assisted in the selection of cases and in contact with patients.

INCIDENCE OF CAVUM SEPTI PELLUCIDI AND CAVUM VERGAE IN 1,032 HUMAN BRAINS

JESS T. SCHWIDDE, M.D.
IOWA CITY

IN THE midline of the brain are two potential spaces which occasionally may dilate to an abnormal degree, simulate tumor, and produce severe neurological symptoms. They present a pathognomonic ventriculogram and are successfully treated by rupture of their membranes through a parietal trephine opening (Miller [1]). The purpose of this communication is to present the results of a study of the incidence of the cavum septi pellucidi and cavum Vergae in 1,071 consecutive brains.

The septum pellucidum is a thin vertical partition which rostrally separates the bodies of the lateral ventricles (Fig. 1). This somewhat triangular membrane, consisting of two glial layers, is attached anteriorly and superiorly to the corpus callosum, and inferiorly and posteriorly to the anterior commissure and anterior limbs of the fornix (Fig. 2). Occasionally the two thin plates of neural tissue are separated by a cavity of varying width, the cavum septi pellucidi, or "fifth ventricle" (Fig. 3). A caudal extension of this cavity from the fornix to the splenium of the corpus callosum is termed the cavum Vergae, or "sixth ventricle" (Fig. 4).

The boundaries of the cavum septi pellucidi are as follows: anteriorly, the genu of the corpus callosum; superiorly, the body of the corpus callosum; posteriorly, the anterior limb and the pillars of the fornix; inferiorly, the rostrum of the corpus callosum and the anterior commissure, and, laterally, the leaves of the septum pellucidum.

The cavum Vergae has the following boundaries: anteriorly, the anterior limb of the fornix; superiorly, the body of the corpus callosum; posteriorly, the splenium of the corpus callosum, and inferiorly, the psalterium (lyra Davidis) and the hippocampal commissure, the fibers of which bridge the space between the diverging posterior pillars of the fornix and rest on the tela choroidea.

Anatomists and embryologists have studied the septum extensively in lower forms, where it is considered to serve as an intermediate station for olfactory impulses. The cavum septi pellucidi, briefly described in most textbooks, has been known at least since the 15th century (Mettler [2]). The cavum Vergae is named for an Italian anatomist whose observations were reported in 1851 (Dandy [3]).

From the Department of Surgery, Division of Neurosurgery, State University of Iowa.

1. Miller, D.: Cysts of the Fifth Ventricle Treated by Intraventricular Drainage: Case, J. Neurosurg. **6**:332-333 (July) 1949.

2. Mettler, C. C.: History of Medicine, Philadelphia, The Blakiston Company, 1947, p. 40.

3. Dandy, W. E.: Congenital Cerebral Cysts of Cavum Septi Pellucidi (Fifth Ventricle) and Cavum Vergae (Sixth Ventricle): Diagnosis and Treatment, Arch. Neurol. & Psychiat. **25**:44-66 (Jan.) 1931.

There are two divergent theories concerning the embryology of these cavities (Thompson [4]). According to one, the cavum septi pellucidi is a portion of the intercerebral fissure which has been shut off by the concrescence of the cerebral hemispheres and the development of various commissures. According to the other, the cavum arises by interstitial cleavage in the rapidly widening lamina terminalis during the third month of embryonic development.

Most observers agree that these cavities are not a portion of the ventricular system and that it is inadvisable to retain the terms "fifth and sixth ventricles."

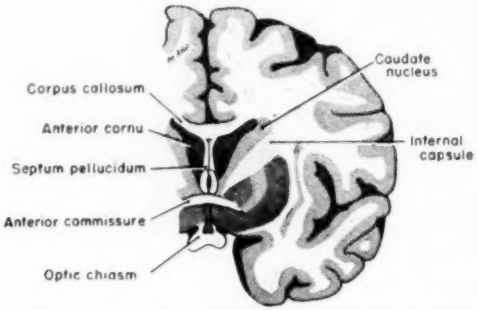


Fig. 1.—Coronal section through the optic chiasm and anterior commissure showing relation of the septum pellucidum to the corpus callosum and anterior horns of the lateral ventricles.

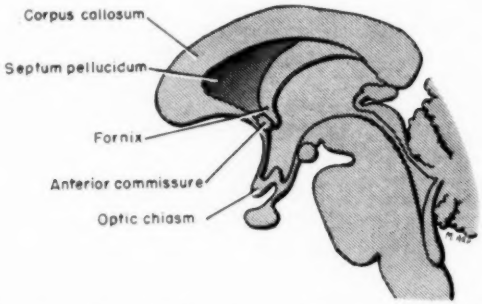


Fig. 2.—Drawing of a median sagittal section of the brain stem illustrating relation of the septum pellucidum to the corpus callosum, anterior commissure, and columns of the fornix. The cavum Vergae is formed in the posterior portion of the septum pellucidum between the diverging columns of the fornix and the corpus callosum.

The cavities differ from the ventricles in embryonic derivation, communicate with the ventricles only under abnormal conditions, and are not lined with ependyma. Wolf and Bamford [5] reported that the walls were composed of a mat of glial fibers with strips of cuboidal cells which did not contain cilia or blepharoplasten. They found no such cellular elements in nine solid septa examined. There has been no

4. Thompson, I. M.: On the Cavum Septi Pellucidi, J. Anat. **67**:59-77 (Oct.) 1932.

5. Wolf, A., and Bamford, T. E.: Cavum Septi Pellucidi and Cavum Vergae, Bull. Neurol. Inst. New York **4**:294-309 (Oct.) 1935.

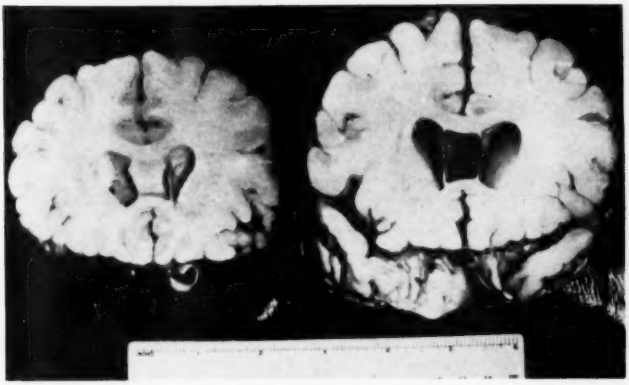


Fig. 3.—Coronal sections of the human brain illustrating a well-developed cavum septi pellucidi and its posterior extension, the cavum Vergae.

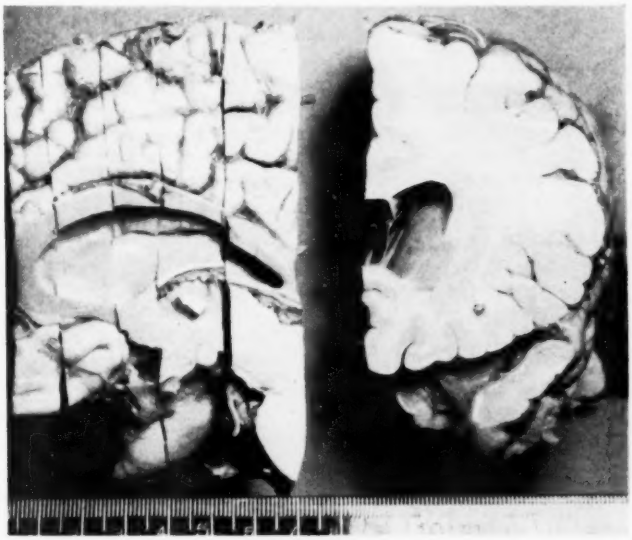


Fig. 4.—Coronal section of the left hemisphere of the same brain as that shown in Figure 3. The right hemisphere has been turned to provide a median sagittal view of the large cavities within the septum pellucidum. The posterior portion between the columns of the fornix and the corpus callosum is known as the cavum Vergae. When the interventricular foramen, shown above, is occluded by this expanding cyst, symptoms of increased intracranial pressure appear.

satisfactory explanation for the source of the fluid found in these cavities. Van Wagenen and Aird [6] believed that the fluid was elaborated by embryonic rests of pia-arachnoid present on the inner walls of the septum. Wolf and Bamford [5] found no cells of mesodermal origin along the lining of the cavity.

Three types of dilatation of the cavum septi pellucidi and the cavum Vergae have been described: (1) noncommunicating, in which the walls of the cavity are intact; (2) communicating, in which an opening or openings exist between the cavity and the lateral or third ventricles, owing to rupture from increasing intracystic tension; (3) acquired or secondary, as a part of a later-developing internal hydrocephalus.

The noncommunicating types are of clinical significance because they may obstruct the interventricular foramina or aqueduct, with resultant increased intracranial pressure, headaches, convulsions, and mental symptoms. Meyer,[7] credited with the first report, and Pendergrass and Hodes [8] have presented the roentgenographic findings in the cavum septi pellucidi and cavum Vergae following pneumoencephalography and ventriculography.

One aspect of this problem, the incidence of these cavities, has received little attention. Van Wagenen and Aird [6] stated that in 30 brains "a dilatation of the cavity of the septum pellucidum of one sort or another was demonstrated in eighteen, or sixty per cent." They believed that it was exceptional for the septum to be formed without such a cavity and that the cavity is much more readily observed in unfixed brains than in formalin-fixed specimens. On the other hand, Dandy [3] held that in most adult brains the spaces are absent, or at most potential.

PRESENT INVESTIGATION

The results of examination of 1,071 consecutive brains obtained from the department of pathology of the State University of Iowa College of Medicine from March, 1947 to May, 1951 are reported. The specimens were fixed for approximately 10 days in 10% formalin and then sectioned in the coronal plane. Determination of the presence or absence of septal cysts was not possible in 39 specimens.

The age, sex, and color of the patient were recorded. Pertinent clinical and necropsy findings, including congenital anomalies, were noted. No correlation with the presence or absence of these cavities was apparent. (The number of colored patients admitted to University Hospitals is so small that no conclusions concerning the racial factor are warranted.)

The septum was examined for a septal cyst or cavum Vergae. When such a cavity was observed, the diameters were measured. Any grossly macroscopic septal separation was included. The average transverse, vertical, and longitudinal diameters for the cavities for the septum pellucidum were 3, 6, and 7.5 mm. respectively; and when there was an associated cavum Vergae the average measurements were 6, 9, and 25 mm. The largest dilated cavity measured 20 by 25 by 68 mm. (Figs. 3 and 4). In the adult brain, the distance from the genu of the corpus callosum to the splenium is about 60 mm., and the maximum longitudinal diameter of each of these cavities is about 30 mm.

Of the 1,032 specimens which were considered suitable for examination, cavities of the septum pellucidum were encountered in 210 (20.34%). Of these, 145 (69.04%) occurred in brains from males and 65 (30.96%) in brains from females. Of the

6. Van Wagenen, W. P., and Aird, R. B.: Dilatations of the Cavity of the Septum Pellucidum and Cavum Vergae: Report of Cases, Am. J. Cancer **20**:539-557 (March) 1934.

7. Meyer, E.: Die Erweiterung des Ventriculus septi pellucidi, Arch. Psychiat. **91**:9-36 (Aug.) 1930.

8. Pendergrass, E. P., and Hodes, P. J.: Dilatations of the Cavum Septi Pellucidi and Cavum Vergae, Ann. Surg. **101**:269-295 (Jan.) 1935.

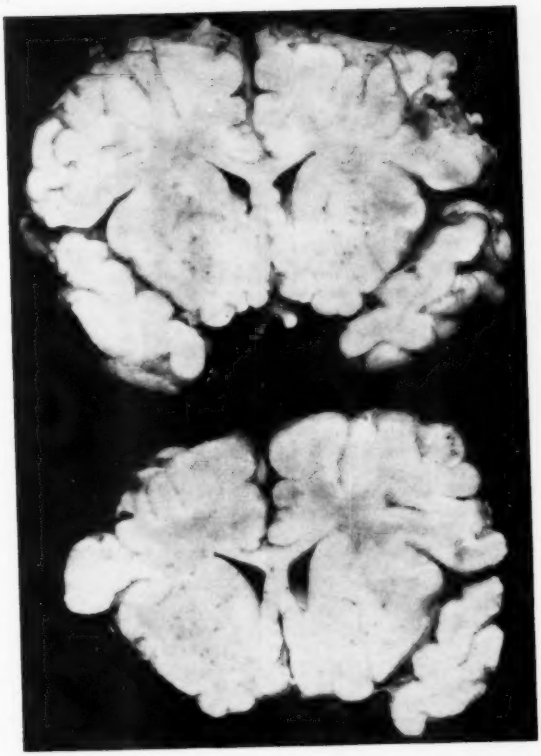


Fig. 5.—Coronal sections of the brain of a stillborn male infant illustrating absence of a macroscopically visible septal separation.

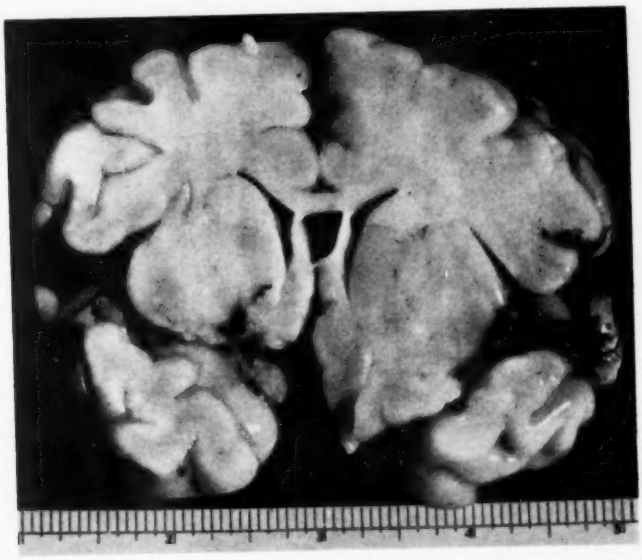


Fig. 6.—Coronal section of the brain of a stillborn male infant illustrating a well-developed cavum septi pellucidi.

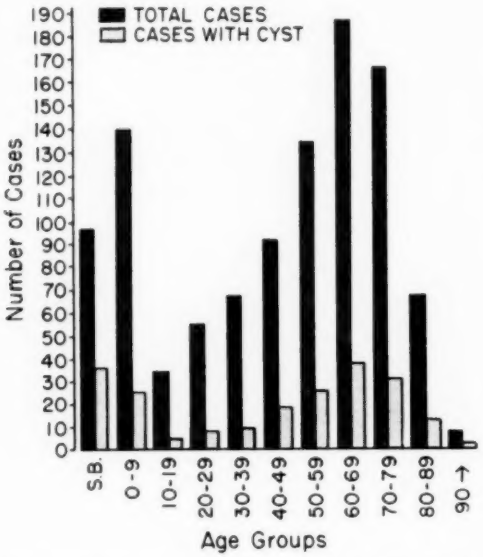


Fig. 7.—Graph illustrating the age distribution in 10-year intervals, for the entire autopsy group and the brains with cysts of the septum pellucidum. In this Figure, and in Figures 8, 9, and 10, *S. B.* refers to deaths of stillborn, premature, newborn, and full-term infants.

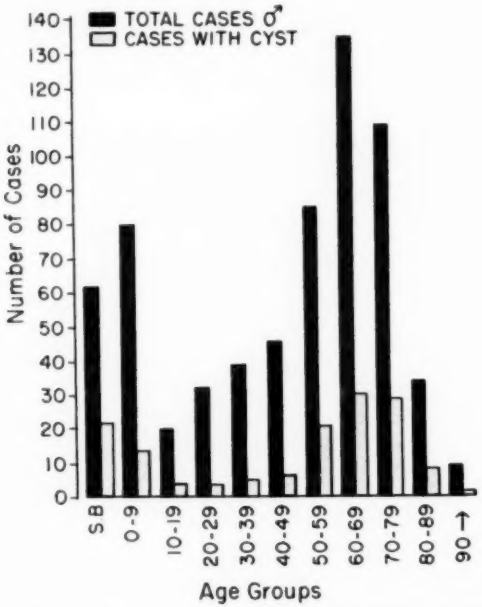


Fig. 8.—Graph comparing the number of brains of males with septal cysts and the number of brains of males in the autopsy group at 10-year intervals. There is a striking number of males in the fifth, sixth, and seventh decades of life in this autopsy series. Compare with the graph for females in Figure 9.

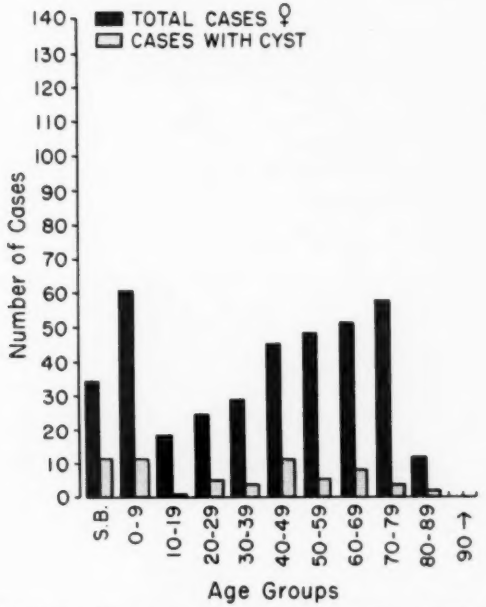


Fig. 9.—Age distribution for brains of females from the entire autopsy series as compared with the age distribution for brains of females with septal cysts.

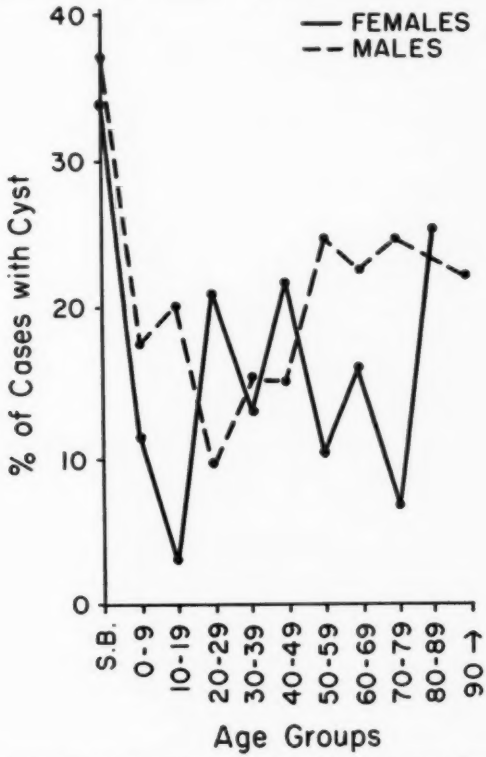


Fig. 10.—Comparison of the percentage of brains with septal cysts, from both males and females in the neonatal and stillborn (premature and full-term infants) groups and at 10-year intervals thereafter.

1,032 specimens, 650 (62.99%) were from males, and the remaining 382 (37.01%), from females. Of the 650 brains from males, 145 (22.30%) contained a cyst of the septum pellucidum, an incidence slightly higher than the 65 (17.01%) encountered among the 382 brains from females.

Of the 1,032 brains, 24 (2.32%) exhibited a cavum Vergae. Of the 145 brains from males exhibiting a cavum septi pellucidi, 17 (11.72%) also presented a cavum Vergae. Similarly, of 65 brains from females exhibiting a cavum septi pellucidi, 7 (10.76%) also presented a cavum Vergae. In no instance was the cavum Vergae found to exist alone.

Dandy [4] stated that Tenchini reported a cavum Vergae in 4% of males and 9% of females and that it was a constant feature in fetuses and newborn infants. In this series no cavity of the septum pellucidum or cavum Vergae was observed in 65 brains from stillborn infants and infants who died in the neonatal period. In Figure 5 coronal sections from the brain of a stillborn white male infant illustrate the absence of a macroscopically visible septal cyst. In Figure 6 is reproduced a coronal section from the brain of another stillborn male infant presenting a well-developed septal separation.

The incidence of septal separation among 1,032 specimens, as encountered in stillborn (premature and full-term) infants, in infants who died in the neonatal period, and in brains from age groups representing 10-year intervals thereafter is illustrated in Figure 7. Figure 8 illustrates the incidence of septal cysts in brains from males arranged in the same age groups. A comparable analysis of the incidence in females appears in Figure 9. In Figure 10 is presented a comparison of the percentage of brains with a septal cyst occurring in the series of 1,032 brains of males and of females in neonatal and stillborn (premature and full-term) infants and at 10-year intervals thereafter. No significant difference in percentage incidence based on age distribution is apparent between males and females.

SUMMARY

The anatomy, embryology, history, and characteristics of cavum septi pellucidi and cavum Vergae are briefly discussed.

Of 1,032 formalin-fixed human brains, 210 (20.34%) presented cavities of the septum pellucidum, with an incidence slightly higher in the male.

Twenty-four (2.32%) brains also presented a posterior extension, or cavum Vergae, with an approximately equal incidence in the two sexes. In no case was the cavum Vergae found to exist alone.

Clinical data and necropsy observations, including the presence of congenital anomalies, were noted, but there was no apparent correlation with the presence or absence of these cavities.

The diameters of these cavities were recorded.

Contrary to the belief of some observers, septal cysts are not a constant finding in the newborn, as evidenced by the finding of 65 brains from stillborn infants and infants dying in the neonatal period in which no cavity of the septum pellucidum or the cavum Vergae was observed.

Bar graphs are constructed to show the age distribution of the cysts at 10-year intervals in males and females and in the combined autopsy group.

When the percentage of brains with cysts, for males and females, are compared on a graph at 10-year intervals, no significant difference is apparent.

OCCLUSIVE CEREBROVASCULAR DISEASE SIMULATING BRAIN TUMOR

Angiographic Differentiation

GORDON L. SMILEY, M.D.
SAGINAW, MICH.

DIFFERENTIATION of stroke from brain tumor, made on the basis of historical data and neurologic findings, is speculative at best. Variations in the clinical pattern of each condition are so infinite that the usual criteria relied upon for selection of surgical candidates are too frequently misleading. Patients with occlusive cerebral disease may manifest gradual or recrudescent development of seizures, hemiparesis, hemianopsia, or aphasia, and may occasionally show papilledema.[1] The precipitous onset of symptoms in some cases of brain tumor is common experience and is often explained by aberrant vascular phenomena in relation to a growing neoplasm, i. e., hemorrhage or venous stasis. When the clinical manifestations of these separate pathologic entities are considered simply as outward expressions of altered neurophysiology, the appearance of one in the guise of the other becomes readily understandable. It is to be acknowledged that the differential criteria are reasonably accurate at the extremes of the continuum over which these differentiations overlap. However, in the great midfield of simulation, accuracy falls abruptly and the clinician is confused. Since occlusive states may be attended by ipsilateral cerebral edema of severe degree, producing pineal and ventricular shift, craniotomy is sometimes undertaken, and failure to find a neoplasm puzzles and embarrasses the sensitive neurosurgeon.

Cerebral angiography has provided an accurate method for determination of the precise diagnosis in those cases of vascular occlusion and/or attenuation which are presented as diagnostic problems or as suspected cases of brain tumor. The method is of particular importance in those cases with ipsilateral edema in which the condition might be interpreted, ventriculographically, as brain tumor. Angiography is at least as sensitive as ventriculography in revealing hemispheral shift, and it has the additional advantage of providing important etiologic information. Angiographic evidence of high-grade or complete occlusion of the carotid artery or the middle cerebral system is sufficient to explain hemispheral shift and is entirely compatible with shift. Although spontaneous intracerebral hemorrhage may be associated with attenuation of cerebral vessels, actual occlusion is uncommon in hemorrhagic stroke. In cases of stroke the major vessels are usually patent enough to reveal regional dislocation. In my experience, hemispheral tumors do not cause attenuation of the vessels, in spite of severe dislocation, condensation, and stretching. Occlu-

From the Department of Surgery, Division of Neurosurgery, State University of Iowa College of Medicine.

1. Sorgo, W.: Über den durch Gefässprozesse bedingten Verschluss der Art. carotis interna, Zentralbl. Neurochir. **4**:161-179 (July) 1939.

sion of the carotid siphon or its major divisions may occur in connection with ruptured aneurysm involving these vessels, and angiographic delineation of intracerebral clots may be rendered difficult, since displaced vessels are not demonstrated. Most of these clots are located in the temporal lobe, however; and since thrombus propagation distal to aneurysms commonly spares at least one trunk of the middle cerebral system, there is usually a patent channel revealing pathognomonic dislocation. Ruptured aneurysm of the anterior segment of the circle of Willis may induce occlusion of the ipsilateral anterior cerebral artery and may be the source of intrafrontal hemorrhage. Bilateral angiography should provide all the necessary information for differentiating these states, since the paired anterior cerebral arteries are symmetrically located in the midline. Moreover, in spite of distal thrombus propagation, aneurysms are usually demonstrated, and this clue alone should suggest the possibility of intracerebral hemorrhage. Extreme narrowing of the basilar portion of the carotid tree following spontaneous subarachnoid bleeding is presumed to represent spasm. This condition may persist for two to three weeks and should not be confused with intrinsic cerebroarterial disease.

It is the purpose of the present discussion to emphasize the role of diffuse, intrinsic attenuating and/or occluding disease of the carotid system in the production of clinical syndromes simulating brain tumor and to establish carotid angiography as a reliable method of differentiation. Although periarteritis, thromboangiitis, syphilis, and arteriosclerosis have been described in causal relation to these states, the cause of many of them remains obscure. Isolated involvement of a single carotid tree is common, and evidence of generalized arterial disease is often lacking. Since these attenuating processes are often gradually progressive, it is not surprising that the alterations of cerebral function produced by resultant ischemia parallel those of cerebral neoplasm, particularly when unilateral cerebral edema and infarction ensue in advanced stages of occlusion.

Restriction of angiography to problem cases represents inadequate sampling of tumor-suspect material. Although angiography will usually decide the diagnostic issue in these particular cases, its restriction to such cases will leave in error the diagnosis in others, which are considered more typical of tumor. This has become apparent in the clinic of this hospital since the adoption of angiography for verification and localization of most clinically lateralized tumors.

Simplified percutaneous angiography, as perfected in this clinic,[2] requires but one operator and no sterile nurse. The time consumed is generally much less than is necessary for open angiography; precious operating-room time is saved, and the percentage of successful angiograms is high. Since technical difficulties have been minimized, the procedure is approached with much the same facility as pneumoencephalography, myelography, or other diagnostic tests which long ago became standard practice. During the past year, in only 3 of a total of 85 cases was operation done by the open method because of failure with the closed method.

It is the conviction of my colleagues and myself that untoward reactions in cases of hemispheral tumor are much less common after angiography than after pneumography. This fact has often permitted a delay following angiographic identification and localization of a neoplasm, whereas pneumography previously committed one to the performance of craniotomy on the same day. We are grateful for

2. Smiley, G. L.: Simplified Percutaneous Angiography, Journal-Lancet, to be published.

the flexibility thus allowed in the scheduling of operating-room time. Despite the general feeling that angiography may occasionally accelerate the downward course of the patient with an occlusive lesion, our experience leads us to believe that it has not altered the ultimate outcome by more than several hours or days. Patients who have appeared to react unfavorably have been desperate at the time of angiography, and their continued deterioration has simply represented a projection of the previous trend. Absence of unfavorable reactions in most patients having these lesions would seem to lend substance to this impression. Since all occlusive lesions which are detected angiographically are from cases of suspected hemispheral tumors, suspected ruptured aneurysm, and tumor-occlusion problems, we see no present means of completely obviating the objectionable reactions, except through abolition of the procedure. Certainly, its advantages far outweigh its disadvantages. Albeit, we are keenly aware of the need for a less noxious contrast medium.

Although it has not been our practice to perform routine stellate-ganglion block before angiography, we have occasionally done it in cases presenting a diagnostic problem and in senile patients, and we believe that such block should be performed soon after identification of occlusive disease. Papaverine is recommended by many authors and may be effective in minimizing the insult of angiography to an already embarrassed hemicerebral circulation.

Whereas I have taken the position that routine angiography will avoid unnecessary craniotomies in the aforementioned groups of cases, I do not take the absolute view that surgery is completely without benefit for those patients who show severe hemispheral shift in relation to such lesions. Decompression may be life-saving for such patients. This is suggested by the course of events in Case 1.

REPORT OF CASES

Case 1.—A farmer, aged 50, was admitted to the State University of Iowa General Hospital on Nov. 7, 1950. Three weeks before admission, while driving he made a left turn and drove into a ditch. He later stated that this accident had been associated with a blackout, but he could not be sure whether syncope had preceded or followed the accident. He declared that he was conscious during the accident, turned out the car lights afterward, and walked away for a distance of 300 ft. (9 kilometers). He denied having received head trauma. Examination by his local physician revealed nothing abnormal. One week later he was noted to behave peculiarly. While working in the field, he zigzagged and could not keep one direction. Reexamination by his physician revealed left hemiparesis, and he was told that he had suffered a light stroke. Hemiparesis progressed gradually; mental confusion and disturbed, combative behavior ensued.

On his admission, examination revealed a blood pressure of 160/80, a pulse rate of 96 per minute, and a temperature of 98.8 F. He was drowsy, restless, only partially oriented, and combative when stimulated. Moderate left hemiparesis was present, and there was obvious left homonymous hemianopsia to confrontation tests. Except for mild paresis of the left side of the face, the cranial nerves were intact and the optic fundi normal. Although tone was diminished in the left extremities, there were bilaterally equivalent hyperreflexia and bilateral sustained ankle clonus. A positive Babinski response was elicited on the left side, and Rossolimo's sign was present bilaterally. Elicitation of superficial reflexes and sensory examination were unsatisfactory because of lack of cooperation. However, there was no gross defect in appreciation of pinprick. The peripheral vessels were considered normal.

Laboratory findings were normal except for cerebrospinal fluid protein of 74 mg. per 100 cc. The cerebrospinal fluid pressure was not recorded; the patient was uncooperative. Roentgenograms of the skull and chest were normal.

In view of his automobile accident, the subsequent time interval, and his partial amnesia for events surrounding the ditching, chronic subdural hematoma was considered. Cerebral neoplasm and vascular disease were mentioned as being less likely diagnoses, although the possibility of a cerebral lesion antedating his accident was recognized. The latter suspicion arose

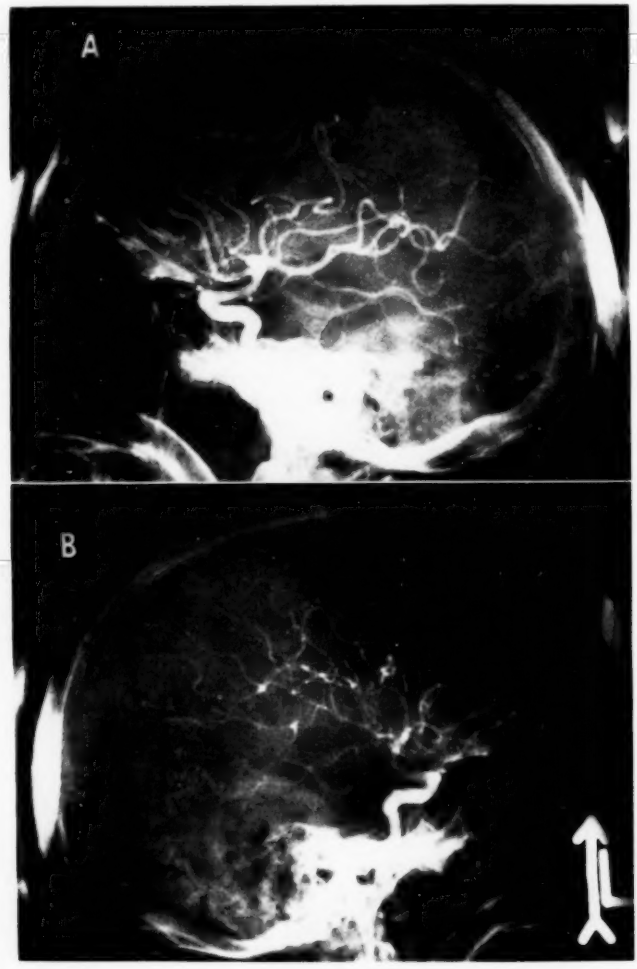


Fig. 1 (Case 1).—Arteriograms. *A*, left middle cerebral system; *B*, right middle cerebral system.

from the knowledge that he had turned left into the ditch, and he was subsequently found to have left hemianopsia.

Bilateral percutaneous carotid angiography on Nov. 8, 1950, revealed no significant displacement of the cerebral vessels from their anatomic locations. The right middle cerebral system appeared diffusely and strikingly attenuated as compared with its left counterpart (Fig. 1*A*

and *B*). The inferior trunk was occluded distal to the trifurcation (Fig. 1*B*). No evidence of hemispheral shift was demonstrated.

On the day following angiography the patient became alert, completely cooperative, and no longer confused. Mild hemiparesis and complete hemianopsia persisted. Stellate-ganglion blocks did not appear to hasten his subsequent spontaneous improvement. He was discharged on November 24, with only slight residual hemiparesis, but still with complete hemianopsia. Mental status and personality were approximately normal.

He was readmitted Dec. 4, 1950, having experienced gradual recurrence of confusion and increasing hemiparesis. Examination revealed that he was deeply stuporous and that the left extremities were paralytic; a mild Babinski response was elicited on the left, and a frank Babinski response, on the right. The blink reflex was absent when threatening stimuli were applied from the left. Papilledema was not noted. The blood and urine were normal. The temperature was 99.2 F. rectally. Blood pressure was 120/80. The pulse rate was 64 per minute. The respiration rate was 20 a minute. The cerebrospinal fluid pressure was 260 mm. of water. The protein content of the cerebrospinal fluid was 168 mg. per 100 cc.

Fig. 2 (Case 1).—Anteroposterior projection showing severe hemisphere shift.

Because of the gradual progression of the right cerebral disability to an advanced morbid state, it was considered by all members of the department, except myself, that the previous diagnosis of occlusive middle cerebral artery disease was mistaken, and an impression of neoplasm of the right cerebral hemisphere, probably a temporoparietal glioma, was substituted. Ventriculographic study on Dec. 7 revealed pronounced ventricular shift from right to left without significant local ventricular deformity. The third ventricle was convexly distorted to the left in anteroposterior projection (Fig. 2), suggesting a temporal or temporoparietal mass lesion. These findings were so gross that I suffered temporary loss of faith (and face) in angiographic diagnosis.

Craniotomy, on Dec. 7, did not disclose a neoplasm. Swelling of the right cerebral hemisphere was so severe as to preclude replacement of the bone flap. Transcortical incision through the midtemporal gyrus to a depth of 8 cm. revealed only very edematous, softened white matter. A similar incision into the inferior parietal region revealed greater softening. Biopsy specimens were taken, which were reported as showing inflammatory changes and gliosis, with marked perivascular infiltration of chronic inflammatory cells. No endarteritis or arteriosclerosis was seen.

After a difficult postoperative period, his condition improved; hemiparesis subsided, and consciousness returned. On Dec. 19, he was fully conscious; speech was coherent, but he remained

highly confused. Motion of the left extremities was vigorous. The scalp overlying the decompression area was slightly sunken. Later, he walked with a hemiparetic gait and had fair use of the right upper extremity, but intermittent mental confusion, disorientation, and disturbed behavior persisted, necessitating transfer to a state psychiatric hospital. At the time of discharge, on Jan. 11, 1951, his scalp was deeply sunken. This finding, most will agree, belies the presence of hemispheral tumor.

In view of the histologic findings in this case, encephalitis must be considered, although these changes are compatible with infarction and the angiographic evidence for attenuation of the middle cerebral system with occlusion of one of its trunks tends to favor intrinsic vascular disease. It is conceivable, and within clinical experience, that some of these entities are acute and not irrevocably progressive, especially those which show perivascular inflammatory infiltrates. A lesion of this type may

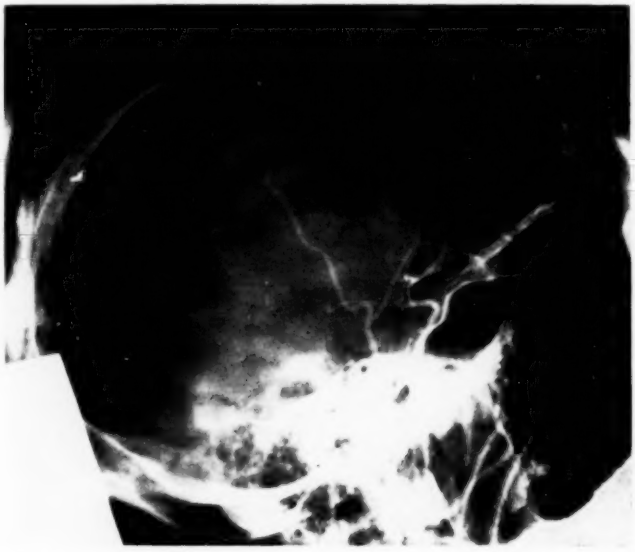


Fig. 3 (Case 2).—Arteriogram of the left cerebral system, lateral projection.

explain his partial recovery, and it would seem that decompression was of timely, although uncalculated, benefit.

Case 2.—A farmer, aged 43, was admitted to the State University of Iowa General Hospital on April 16, 1951, in a state of stupor, aphasia, and right hemiplegia. A history of headaches since 1948 was elicited. These headaches were nucho-occipitovertical and often unilateral, although either side might be affected. At first they were most intense in the afternoon, after hard work, but more recently they had been more manifest in the early morning.

In June, 1950, he experienced a Jacksonian seizure on the right side, followed by aphasia, right hemiparesis, and hemisensory impairment. These defects disappeared gradually after two to three weeks. His physician noted that his blood pressure was elevated.

After this attack, his headaches became intensified and more frequent, and he experienced vertigo several times a day. Sudden motion and head turning aggravated his dizziness.

On Jan. 2, 1951, he began having two to three Jacksonian seizures daily on the right side. These were attended by intense left-sided headache and were followed by transient speech disturbance, paresis, and numbness of the right extremities.

In another hospital, complete diagnostic studies revealed only mild, labile arterial hypertension, an atrophic left kidney, and very slight evidences of the neurologic defects noted above plus right homonymous inferior quadrantanopsia. Ventriculograms and angiograms of the left carotid system were interpreted as showing a normal condition, and he was discharged from that hospital under anticonvulsant-drug therapy.

Upon his return home, his seizures and headaches did not abate. Loss of weight, general weakness, and drowsiness developed. On April 13 he experienced a seizure of greater magnitude, clonic jerking being bilateral and associated with loss of consciousness. After this attack, aphasia was severe, and impairment of the right extremities progressed to complete hemiplegia within a few days. He became incontinent and stuporous.

The blood pressure was 168/140. The temperature was 101 F. rectally. The pulse rate was 100 per minute. The respiration rate was 22 a minute. Moderate stupor and total expressive aphasia were apparent. Understanding of speech seemed severely limited. Examination of

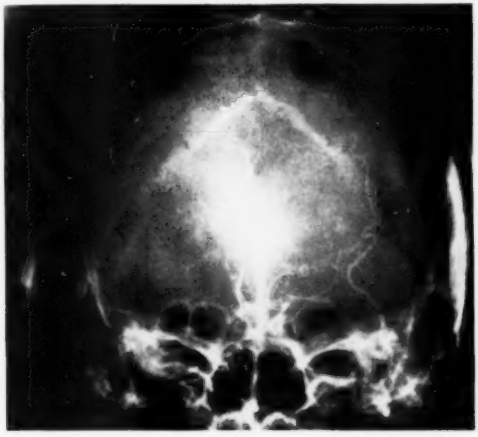


Fig. 4 (Case 2).—Anteroposterior projection, with left anterior cerebral artery showing shift from left to right.

visual fields was unsatisfactory. The optic fundi showed only minimal evidence of hypertensive retinopathy. Hemiplegia and hemianesthesia were virtually complete on the right, with hyperreflexia, pathologic finger and toe reflexes, ankle clonus, and absence of superficial reflexes on the right side.

The urine was normal. A blood count showed 4,370,000 red cells, 14 gm. of hemoglobin per 100 cc., and 22,250 white cells, with 73 polymorphonuclear neutrophiles, 18 lymphocytes, 8 mononuclear cells, and 1 eosinophile. Cerebrospinal-fluid examination revealed a pressure of 160 mm. of water, 41 cells (mononuclear) per cubic millimeter, a negative Pandy reaction, a total protein content of 46 mg. per 100 cc. A roentgenogram of the skull revealed a pineal shift to the right; a roentgenogram of the chest showed nothing abnormal.

The provisional diagnosis of brain tumor was recorded by three separate examiners.

On April 17, percutaneous angiography of the left carotid system revealed attenuation of the internal carotid artery in the neck and intracranially. The left anterior cerebral artery was filiform, and the middle cerebral system was completely occluded except for one thread-like vessel (Fig. 3). In anteroposterior projection the left anterior cerebral artery demonstrated hemispheral shift from left to right (Fig. 4). The external carotid branches were not attenuated and were unusually well demonstrated, presumably because of retarded flow through the internal

carotid tree. The hemispheral shift was attributed to infarction and edema, and craniotomy was not undertaken. Although there was no immediate untoward reaction following angiography, the patient's condition continued to deteriorate, and he died on April 18, 1951.

Autopsy disclosed extensive generalized arteriosclerosis with particularly severe involvement of the aorta and valves, the pulmonary arteries, and the cerebral arteries. There were massive infarction and swelling of the left cerebral hemisphere, including the thalamus and basal ganglia and sparing only the prefrontal area. Both old and recent punctate hemorrhages were seen along the cortical distribution of the left anterior cerebral artery and in the midbrain. The left internal carotid tree showed multiple atherosclerotic plaques and diffuse narrowing of lumens, with high-grade obstruction at the origin of the middle cerebral artery. Other findings were aplastic left kidney with retention cysts, and mesenteric and periaortic lymphadenopathy.

The value of decompression in this case was dubious, in view of the extent of cerebromalacia.

SUMMARY

The two cases reported illustrate graphically that the more or less routine performance of angiography in cases of suspected lesions of the cerebral hemisphere has greatly potentiated the differential acumen of the neurosurgeon. This approach to neurologic diagnosis in such cases has removed much of the element of speculation and has placed this aspect of the specialty on a firmer scientific basis. Unnecessary or contraindicated craniotomy may be avoided, and certain cases in which the angiogram shows occlusion and severe hemispheral shift can be selected for decompression.

SUBARACHNOID HEMORRHAGE, INTRACEREBRAL HEMORRHAGE, AND INTRACRANIAL ANEURYSMS

ANATOLE DEKABAN, M.D.
AND
DONALD McEACHERN, M.D.†
MONTREAL, CANADA

WE HAVE selected 143 cases from the records of the Montreal Neurological Institute for analysis of the relation of spontaneous subarachnoid hemorrhage,[1] intracerebral hemorrhage, and intracranial aneurysm. These cases cover a period of 10 years, from 1938 to 1948.

The criteria for selection were as follows:

1. The condition had to be proved by lumbar puncture, arteriogram, operation, or autopsy.

2. Onset of hemorrhage must have occurred within four days prior to admission.

3. Traumatic cases were excluded.

The material is classified as follows:

		No. of Cases
Ruptured aneurysm		30
Proved at autopsy	26	
Proved by arteriography and at operation	4	
Nonruptured intracranial aneurysm (proved by arteriography or operation)		8
Abnormal arteriovenous communication		13
Proved by arteriography	4	
Proved by arteriography and at operation	3	
Proved by definite signs only, such as bruit or pulsating exophthalmos	6	
Subarachnoid hemorrhage with proved rupture of anatomically normal artery		1
Subarachnoid hemorrhage of undetermined cause		56
Primary intracerebral hemorrhage		35
Proved at autopsy	23	
Proved at operation	12	
Total		143

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

† Dr. McEachern turned over the final draft of the manuscript of this contribution to Dr. Dekaban on Oct. 31, 1951, and a little later in the day died suddenly and unexpectedly while at work.

1. In this paper, subarachnoid hemorrhage is defined as rupture of a blood vessel enclosed by leptomeninges (cortical or basal blood vessels), whether destruction of adjacent brain tissue occurs or not. Primary intracerebral hemorrhage is the result of rupture of a central or perforating artery within the brain tissue.

The data are discussed under three headings: (1) general systemic and local meningeal reactions to blood in the subarachnoid space; (2) statistical considerations and points of interest in the three conditions (subarachnoid hemorrhage, intracerebral hemorrhage, and intracranial aneurysms); (3) treatment.

GENERAL SYSTEMIC AND LOCAL MENINGEAL REACTIONS

General Systemic Reactions.—The presence of fever and polymorphonuclear leucocytosis of the blood is almost the rule. Patients have sometimes been admitted with the diagnosis of acute meningitis. For others the condition has been misdiagnosed as "sunstroke." If this word appears in any patient's history, the possibility of subarachnoid hemorrhage should be considered.

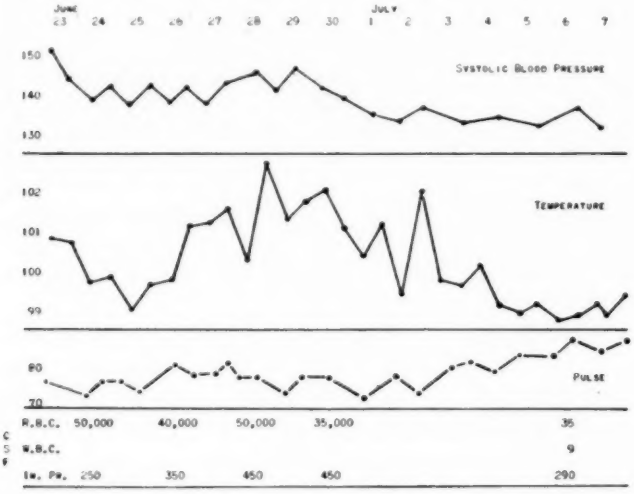


Fig. 1.—Records in an uncomplicated case of frequent occurrence. The temperature and blood pressure at the onset are usually elevated. They drop within the first two or three days, and on the third to the fourth day there is again a rise, which persists for about a week. The pulse is lowered during the rise in blood pressure. The number of red blood cells per cubic millimeter roughly corresponds to the initial pressure of the cerebrospinal fluid.

Recurrent elevation of temperature in the absence of infection signifies repeated bleeding (aseptic meningitis) (Figs. 1, 2, and 3). Of 81 patients, 14 showed a temperature over 102 F. for at least three days; 23 had a temperature over 101 F. for at least three days; 34 had a temperature over 100 F. at least on one occasion, and 10 had a temperature below 100 F. during their whole stay in hospital.

Delirium or comatous state was observed in the majority—75% of 88 patients. The mental condition of the remaining 25% was bright and unclouded, and the correct diagnosis could have been overlooked, since headache, malaise, and fever formed the main part of the picture. In mild cases, when the patient remains at home, the likelihood of lumbar puncture being done is remote, and subarachnoid hemorrhage goes unrecognized.

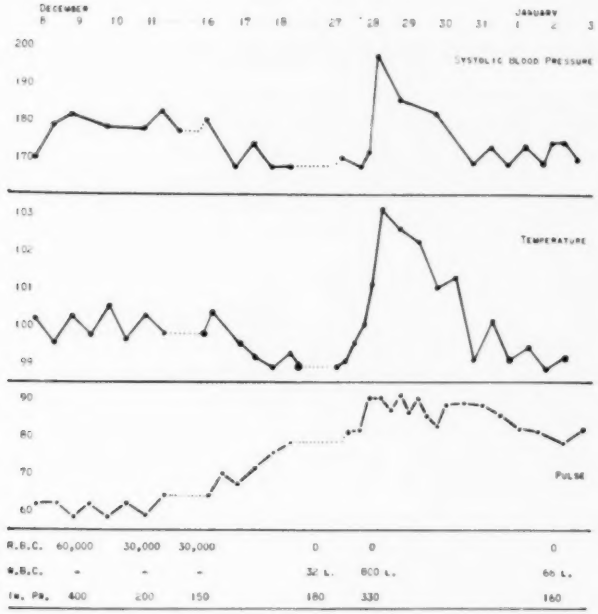


Fig. 2.—Records in a case of aseptic meningitis due to subarachnoid hemorrhage. The meningitis occurred after the red blood cells had largely disappeared from the cerebrospinal fluid.

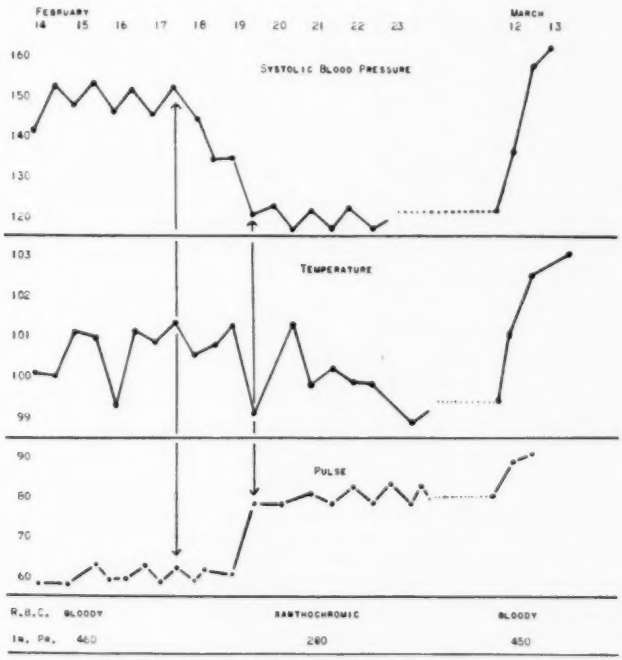


Fig. 3.—Recurrent subarachnoid hemorrhage while the patient was still in the hospital, followed by death. This case demonstrates well the relation of blood pressure, temperature, and pulse in the recovery stage and at the onset of the second hemorrhage.

One-quarter of the patients, or 23 of 88 with spontaneous subarachnoid hemorrhage, had convulsive seizures either at the onset of hemorrhage or shortly thereafter. In 20 patients the seizures were generalized, and in three they were of focal character. The high incidence of seizures is noteworthy.

Meningeal Reaction.—Headache, nuchal rigidity, and a Kernig sign were almost the rule. Vomiting (76%) and photophobia (78%) were present in over three-quarters of the patients.

Cerebrospinal Fluid.—An increase in pressure (above 200 mm. of water) occurred in 81% of the patients. The number of red blood cells per cubic millimeter of cerebrospinal fluid ranged from 5,000 to 100,000.

The degree of pleocytosis did not necessarily parallel the amount of hemorrhage but probably depended upon other factors as well, such as the rate of hemolysis and the formation of altered blood pigment.

The number of white blood cells per cubic millimeter of cerebrospinal fluid in 43 cases of subarachnoid hemorrhage were as follows:

White Cells/Cu. Mm.	No. of Cases
200-4,000	4
50-200	9
10-50	17
Below 10	13

Morbid Anatomy.—Better evidence of the inflammatory reaction to blood in the subarachnoid space is obtained by histopathological methods (Fig. 4*A*, *B*, *C*, *D*, and *E*).

We studied autopsy material from a number of cases in which death occurred from 12 hours to two weeks after onset of hemorrhage. When death occurred within about 18 hours, the reaction was chiefly an increase of polymorphonuclear leucocytes. These were distributed in small collections, together with lymphocytes, around the meningeal blood vessels.

The second day after bleeding these elements increased in number; mesothelial cells and phagocytes also appeared. Up to the sixth day the polymorphonuclear leucocytes dominated the picture. From the eighth day on, phagocytosis subsided, and polymorphonuclear leucocytes were no longer present.

After about two weeks mild fibrosis was observed. This was distributed in a patchy manner, an occurrence which may explain the infrequence of hydrocephalus after subarachnoid hemorrhage.

These findings are in accord with the observations of Finlayson and Penfield [2] in experimental animals and with those of Hammes [3] in human brains.

STATISTICAL CONSIDERATIONS

Of 87 patients with subarachnoid hemorrhage due to various causes (30 with proved ruptured aneurysms, 1 with rupture of abnormal arteriovenous communication, and 56 of undetermined cause), 55 (63%) survived. Of 33 fatal cases, rup-

2. Finlayson, A. J., and Penfield, W.: Acute Postoperative Aseptic Leptomeningitis: Review of Cases and Discussion of Pathogenesis, Arch. Neurol. & Psychiat. **46**:250-276, 1941.

3. Hammes, E. M.: Reaction of the Meninges to Blood, Arch. Neurol. & Psychiat. **52**:505-514, 1944.

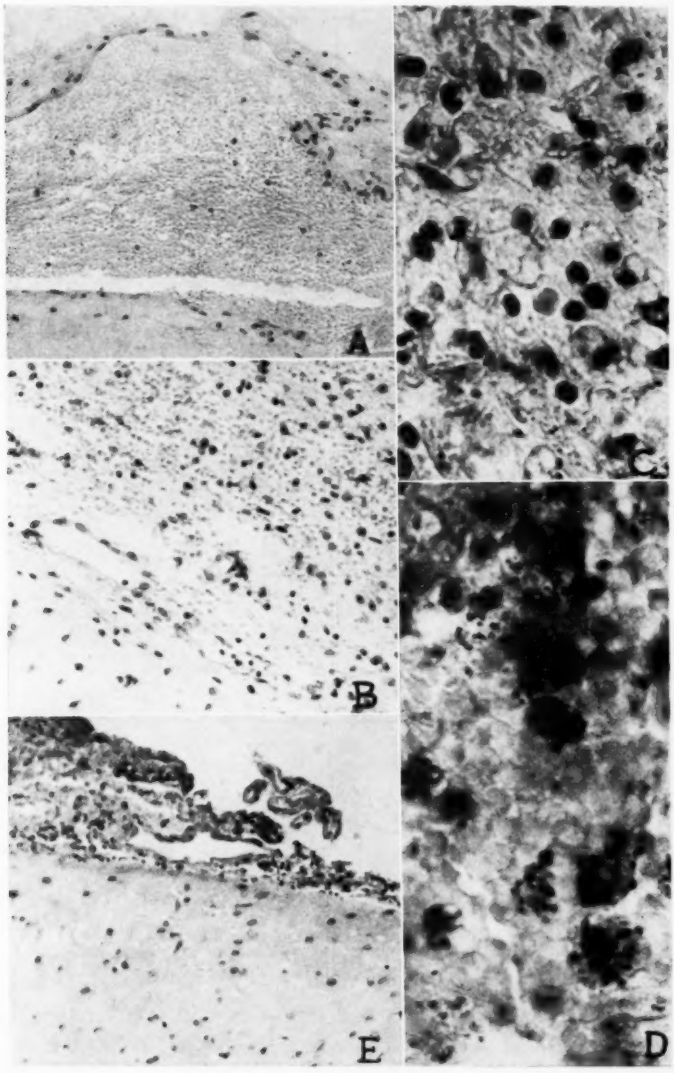


Fig. 4.—*A*, recent hemorrhage, with marked distention of the subarachnoid space with red blood cells.

B, lymphocyte and polymorphonuclear-leucocyte reaction in a case of death after 38 hours.

C, increased cellular infiltration with beginning phagocytosis in a case of death in three days.

D, marked activity of macrophages, which contain pigment and fragments of red blood cells, in a case of subarachnoid hemorrhage, followed by death in eight days.

E, patchy fibrosis of meninges in a case of death of three weeks after subarachnoid hemorrhage. The patchy distribution probably explains the comparatively infrequent occurrence of hydrocephalus as a sequela of subarachnoid hemorrhage.

tured aneurysms were found at autopsy in 26. In one case there was a ruptured, but otherwise normal, artery at the base of the brain. In six cases autopsy was not performed. Richardson and Hyland,[4] in similarly selected cases, found a survival rate of 48%.

Nearly 50% of deaths occurred in the first nine days, the main cause being continous bleeding or massive destruction of brain tissue. From the 10th to the 33d day, the commonest cause of death was recurrent bleeding (24%) and, in a few instances, secondary complications. The exact distribution of cases is shown in the accompanying table.

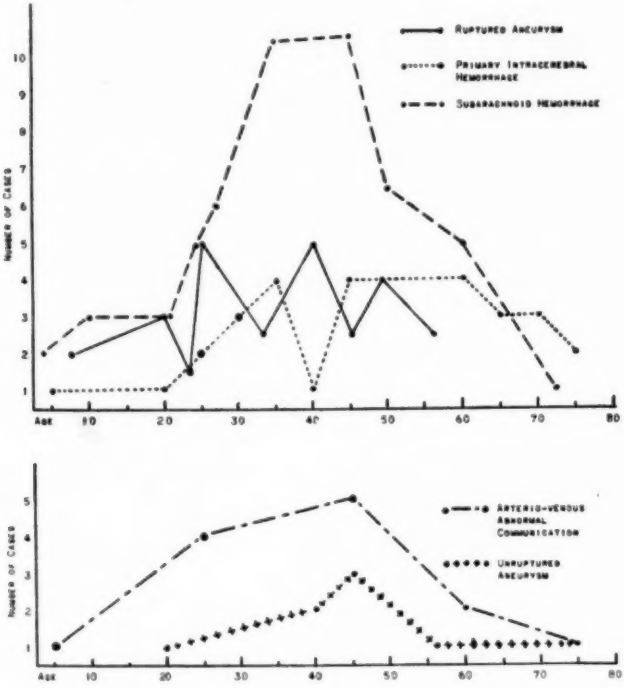


Fig. 5.—Age incidences for ruptured aneurysms, primary intracerebral hemorrhage, and subarachnoid hemorrhage. In all three conditions the peak roughly corresponds to the age group between 30 and 55 years. Subarachnoid hemorrhage and ruptured aneurysm tend to occur in the younger age group; primary intracerebral hemorrhage, in the older age group.

4. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms: Clinical and Pathological Study of Subarachnoid and Intracerebral Haemorrhage Caused by Berry Aneurysms, Medicine **20**:1-83, 1941.

About three-quarters of the ruptured aneurysms were located in the anterior half of the circle of Willis. Four aneurysms were fusiform, and 26 were of the berry type. Of 56 patients with subarachnoid hemorrhage of undetermined cause, 7 showed moderate arteriosclerosis, 2 gave evidence of chronic rheumatic heart disease, and 2 had a history of syphilitic infection, with negative serologic reactions at the time of examination. One patient had mild dyscrasia of thrombocytopenic type. Only one patient had vascular hypertension.

We studied 35 cases of primary intracerebral hemorrhage from the point of view of possible surgical treatment. In 23 autopsy was performed, and the diagnosis in 12 was verified at operation. Of the 12 patients, 10 survived. The commonest sites of bleeding were in the basal ganglia, the frontal lobe, and the parietal lobe.

Certain features differentiate subarachnoid from intracerebral hemorrhage. In the latter, the incidence is higher in the older age group (Fig. 5), and vascular hypertension is much more frequent and the mortality rate higher. This is in accord with the different etiological factors operating in the two conditions. Spontaneous

Survival Period, in Days, from Onset of Subarachnoid Hemorrhage in Thirty-Three Cases

Day	1	2	3	5	7	9	10	14	20	21	26	28	30	31	32	33	49	51	62
No. of cases.....	2*	..	..	..	1*	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	2*	1*	1*	1*	1*	1*	1†	1†	1†	1†	1‡	..	1†	1†	1§	1†	1‡	1§	1§
	2*	..	1‖	1*	1†	..	..	..	..	1†	..	..	..	..	..	..	..	..	..
	1Ξ	..	..	..	..	..	..	1Ξ	..	..	1Ξ	1Ξ	..	..	..	1Ξ	..	..	..

* Ruptured aneurysm; death due to first hemorrhage.
† Ruptured aneurysm; death after recurrent bleeding.
‡ Ruptured aneurysm; postoperative death.
§ Ruptured aneurysm; death due to secondary complication.
‖ Ruptured artery without obvious anatomical lesion.
Ξ Autopsy not done; clinical evidence of subarachnoid hemorrhage.

subarachnoid hemorrhage is usually due to rupture of a congenital aneurysm, whereas intracerebral hemorrhage is oftener due to generalized cerebrovascular disease.

TREATMENT

Ruptured Aneurysm.—Of 30 cases of proved ruptured aneurysm, operation was performed in 9. In six cases operation was preceded by arteriography. In six instances, the aneurysm was clipped, or injured brain tissue was excised together with the ruptured aneurysm. In three of these cases the patients survived. In one instance only extravasated blood was removed, but the patient died and at autopsy a ruptured aneurysm was found. In the two remaining cases ligation of both the internal and the common carotid artery was carried out. One of the two patients survived, and the other died.

Spontaneous Subarachnoid Hemorrhage.—Fifty-seven patients with a diagnosis of subarachnoid hemorrhage of undetermined cause were treated conservatively, with special emphasis on bed rest. Seven of them died, and, unfortunately, autopsy was not performed. This group consisted of patients with normal arteriograms and others for whom arteriograms were not obtained.

Treatment of spontaneous subarachnoid hemorrhage may follow any of three main courses.

1. Conservative Treatment: Strict bed rest of at least six weeks' duration is enforced. When the intracranial pressure is greatly increased, it has been our practice to perform lumbar puncture and to lower the pressure arbitrarily to one-half its previous level. Under this regimen, craniotomy is considered only as an emergency measure.

The possibility that a blood dyscrasia, rather than a faulty blood vessel, is responsible for subarachnoid hemorrhage should always be kept in mind. We do complete hemographic studies in all cases, and we usually prescribe rutin, vitamin K, and ascorbic acid in any event. In three of our cases we have had reason to believe that an abnormal tendency to bleeding was the main factor leading to subarachnoid hemorrhage.

2. Progressive Conservative Treatment: An arteriogram is made as soon as possible. If an aneurysm is present, ligation of the corresponding internal and common carotid arteries is performed at once, followed in some instances by intracranial ligation of the aneurysm after six to eight weeks.

3. Radical Treatment: Immediate arteriography and intracranial clipping or removal of the aneurysm are carried out if possible.

Certain factors, in addition to the mortality rate, have to be considered in choosing a proper course of treatment.

Of 38 patients with ruptured and unruptured aneurysms, 7 had multiple and 3 had bilateral aneurysms. Aneurysms cannot always be visualized by arteriography. Alpers and Ryan [5] reported two cases in which the arteriograms revealed no lesion and aneurysm was later found at operation. Most neurosurgeons have had similar experiences.

It is seldom, if ever, that an arteriogram shows thorotrast* leaking from a ruptured aneurysm. It is therefore apparent that with multiple aneurysms the one visualized by arteriography may not be the ruptured one.

Arteriography, when performed in cases of subarachnoid hemorrhage, should always be bilateral unless there are definite localizing signs. Each case should be carefully considered for the most appropriate treatment.

If the patient is young, operation may be preferable to conservative treatment. The type and location of an aneurysm may determine the surgical step. If an aneurysm is inaccessible, or if its removal would require clipping of a large cerebral artery, with possibility of extensive infarction, ligation of the carotid artery in the neck may be the best procedure. Complete excision of an aneurysm is the treatment of choice, but it cannot always be accomplished.

The mortality rate of surgical procedures for different types and locations of aneurysm must be balanced against that of conservative treatment.

With regard to ligation of the carotid artery in the neck, Sweet and Bennett [6] have shown that the blood pressure in the internal carotid artery distal to ligation is about 50% lower than before the procedure. It is unknown to what extent pressure in the cerebral arteries is affected. In animal experiments such a procedure causes a persistent fall of blood pressure in the circle of Willis of only about 16%. Liga-

5. Alpers, B. J., and Ryan, J. J.: Verified Cerebral Aneurysm with Negative Arteriogram, J. Nerv. & Ment. Dis. **109**:220-225, 1949.

6. Sweet, W. H., and Bennett, H. S.: Changes in Internal Carotid Pressure During Carotid and Jugular Occlusion and Their Clinical Significance, J. Neurosurg. **5**:178-195, 1948.

tion of the artery bearing a ruptured aneurysm may be helpful in controlling hemorrhage, but it is probably not decisive. Furthermore, the possible development of hemiplegia is always a hazard, even when graded compression of the vessel has been carried out previously.

In the present series of 143 patients, 16 ligations of the internal and common carotid arteries in the neck were carried out for various conditions (ruptured and unruptured aneurysms, and abnormal arteriovenous communications). Operation was always performed in two stages. Three patients suffered permanent hemiparesis.

Intracranial Hemorrhage.—Operation was carried out on 14 of 35 patients who had primary intracerebral hemorrhage. On nine patients craniotomy was performed and extravasated blood removed. Three of these patients died. In the remaining five, only burr holes were made, and the blood was aspirated. There were no fatalities. It is hard to tell whether surgical intervention was responsible for a greater degree of recovery than might have been expected from spontaneous healing.

The treatment of intracerebral hemorrhage should usually be conservative. The decision as to whether to operate is difficult. In general, if the patient's condition deteriorates and if there is evidence of high intracranial pressure and admixture of blood in the cerebrospinal fluid, it may be desirable to make burr holes and attempt needle aspiration of the extravasated blood. Sometimes even craniotomy may be indicated, for without surgical intervention some of these patients are doomed to die.

SUMMARY

Analysis is made of 143 cases of subarachnoid hemorrhage, intracerebral hemorrhage, and intracranial aneurysm.

Blood in the subarachnoid space, in addition to raising the intracranial pressure, acts as an irritant, causing general systemic and local meningeal reactions. The latter, in some cases, is severe, with pleocytosis, the number of white blood cells amounting to 4,000 per cubic millimeter of cerebrospinal fluid. Aseptic meningitis, or even constitutional fever, may be suspected wrongly in the mild cases unless lumbar puncture is carried out.

The meninges show cellular infiltration and phagocytosis in the acute stage, followed later by fibrosis, which is patchy. This distribution may explain the infrequent occurrence of hydrocephalus in surviving patients.

Ruptured aneurysm was found to be responsible for the subarachnoid hemorrhage in nearly all cases in which autopsy was performed. Twenty-six of 30 ruptured aneurysms were of the congenital, berry type; the remaining 4 were fusiform and of arteriosclerotic origin.

The main courses of treatment of subarachnoid hemorrhage are outlined. Because of the frequent occurrence of multiple and bilateral aneurysms, the necessity of bilateral angiography is stressed.

The majority of patients with spontaneous subarachnoid hemorrhage recover without surgical treatment; in some patients the risk of repeated bleeding may be abolished by intracranial clipping and excision of an aneurysm.

The possibility of blood dyscrasia and an abnormal bleeding tendency should be kept in mind in all cases of subarachnoid hemorrhage, and appropriate treatment should be carried out with rutin, ascorbic acid and vitamin K.

RATE OF ADVANCE OF HOFFMANN-TINEL SIGN IN REGENERATING NERVES

Further Observations

S. SUNDERLAND, M.D., D.Sc.
AND
K. C. BRADLEY, M.B., F.R.A.C.S.
MELBOURNE, AUSTRALIA

IN AN EARLIER paper published in the ARCHIVES,[1] data were presented relating to the rate of advance of the Hoffmann-Tinel sign in regenerating nerves. From an examination of these data it was concluded that regenerating sensory dendrites grow distally at a progressively diminishing rate. At the same time, attention was directed to the difficulty of obtaining suitable clinical material on which repeated observations could be made at frequent intervals during the critical period of recovery, a difficulty which probably explained why this feature of regeneration was generally neglected. This defect can be remedied only by collecting additional data whenever and wherever the opportunity occurs for conducting successive examinations of suitable clinical material. Nathan and Rennie [2] devoted attention to an evaluation of the Hoffmann-Tinel sign, but in their paper they did not refer to the rate of descent of the sign. In a later paper, Napier [3] illustrated a progressively diminishing rate of advance in two well-documented graphs but dismissed this feature in the text with the general statement:

> In the small number of cases where the readings were numerous enough to justify consideration, a progressive diminution in rate of advance was found. . . . Serial readings were obtained in 17 other cases but although on examination of the figures they showed the same tendency to fall off progressively, too much reliance cannot be placed on them owing to the unavoidable meagerness of the observations.

Napier devoted more attention to the measurement of a mean rate of descent of the Hoffmann-Tinel sign, though the manner in which this was calculated was not

---

From the Department of Anatomy and Histology, University of Melbourne.

This work was aided by a grant from the National Health and Medical Research Council of Australia.

A search of the literature has revealed an earlier description of this sign by P. Hoffmann (Über eine Methode, den Erfolg einer Nervennaht zu beurteilen, Med. Klin. **11**:359, 1915; Weiteres uber das Verhalten frisch regenerierter Nerven und über die Methode den Erfolg einer Nervennaht frühzeitig zu beurteilen, ibid. **11**: 856-858, 1915). For this reason the term Hoffmann-Tinel sign will be used in this paper.

1. Sunderland, S.: Rate of Regeneration of Sensory Nerve Fibers, Arch. Neurol. & Psychiat. **58**:1-6 (July) 1947.

2. Nathan, P. W., and Rennie, A. M.: Value of Tinel's Sign, Lancet **1**: 610-611 (April 27) 1946.

3. Napier, J. R.: Significance of Tinel's Sign in Peripheral Nerve Injuries, Brain **72**: 63-82, 1949.

precisely defined. No reference was made either to the distance over which the rate was measured or to the position of the relevant segment of the nerve in the limb, information which is vital for any consideration of rate of growth.[4] Furthermore, since it is now known that one is dealing with a progressively diminishing rate, the use of mean rates of growth is apt to be misleading, since, unless qualified, they suggest that the rate of advance is constant along the full length of the nerve. On this basis, the rate given would be too slow for the proximal part of the nerve and too fast for the distal portion. It is apparent, however, that Napier also experienced difficulty in making serial observations over long periods of time and that if he was restricted to two widely spaced readings only a mean rate could be obtained. His two graphs are, nevertheless, very instructive in that they confirm a progressively diminishing rate of advance. He reported the additional observation, relevant to the present discussion, that "the rate of descent of Tinel's sign after suture and after physiological interruption differed only slightly."

The object of the present paper is to report serial observations on the advance of the Hoffmann-Tinel sign that were made on three patients with injuries of peripheral nerves one, one, and two nerves, respectively, being involved. The importance of the observations lies in the fact that successive examinations in each patient have provided a series of measurements that are sufficiently numerous to permit a reconstruction of the manner and rate at which the Hoffmann-Tinel sign moved down the nerve.

MATERIAL

Only pertinent details of the case histories are given. Percussion was commenced distally and was applied uniformly. The examiner exercised great caution, when eliciting the sign, to localize the point of application of the mechanical stimulus in order to exclude spread effects. The most distal point at which the sign could be elicited at each examination was confirmed by a number of observers.

CASE 1.—L. H., a youth aged 15, lacerated his right upper arm on broken glass. The brachial artery was severed, and in control of the hemorrhage the median nerve was crushed between the blades of a pair of Spencer-Wells forceps, which were fully engaged. The nerve was not freed until two hours later. This injury resulted in complete interruption of conduction in the nerve. The site of the injury was 358 mm. above the distal wrist crease, from which level was measured the point at which the Hoffman-Tinel sign was elicited. The patient was referred to us for observation 27 days after the injury. The nerve recovered spontaneously and completely.

CASE 2.—J. M., a man aged 55, severed the ulnar nerve 180 mm. above the distal wrist crease when he lacerated his left forearm on broken glass. The nerve was sutured six hours later.

CASE 3.—J. B., a man aged 25, had the musculocutaneous and sural nerves crushed between fine forceps 85 and 200 mm. respectively, above the tip of the lateral malleolus for relief of severe pain in the field of distribution of these nerves.

OBSERVATIONS

Details relating to the progress of the Hoffmann-Tinel sign and the calculated rate of advance in each nerve are given in the accompanying Table, while this information has also been represented graphically in Charts 1 and 2.

4. Sunderland, S.: Rate of Regeneration in Human Peripheral Nerves and an Analysis of the Interval Between Injury and the Onset of Recovery, Arch. Neurol. & Psychiat. **58**: 251-295 (Sept.) 1947.

Details Relating to Advance of the Hoffmann-Tinel Sign and Rate of Regeneration Calculated Therefrom

Case No., Nerve Injury	Days Elapsing Between Crush or Suture and Time of Recording Hoffmann-Tinel Sign	Time (Days)	Corresponding Level (Mm.) Below Level of Lesion at Which Hoffmann-Tinel Sign Was Elicited	Distance Traveled (Mm.)	Rate of Advance of Axon Tips, in Mm./Day
1 Median-nerve crush	27		232		
	34	7	273	41	5.8
	48	14	334	61	4.4
	55	7	358	24	3.4
	62	7	376	18	2.6
	69	7	388	12	1.7
	79	10	395	7	0.7
	80	10	409	14	1.4
2 Ulnar-nerve suture	38		33		
	45	7	47	14	2.0
	62	17	95	48	2.8
	69	7	110	15	2.1
	76	7	120	10	1.4
	83	7	127	7	1.0
	103	20	144	17	0.9
	117	14	155	11	0.8
	132	15	164	9	0.6
	139	7	165	1	0.1
3 Musculocutaneous-nerve crush	10		2		
	28	18	35	33	1.8
	36	8	54	19	2.4
	39	3	59	5	1.7
	45	6	70	11	1.8
	47	2	74	4	2.0
	51	4	82	8	2.0
	57	6	98	16	2.7
	62	5	102	4	0.8
3 Sural-nerve crush	4		6		
	8	4	14	8	2.0
	10	2	17	3	1.5
	20	10	40	23	2.3
	25	5	52	12	2.4
	34	9	68	16	1.8
	46	12	85	17	1.4

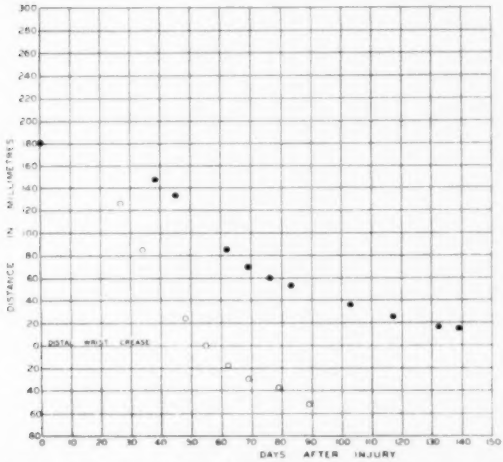


CHART 1.—Advance of Hoffmann-Tinel sign in a case of median-nerve crush (Case 1) and ulnar-nerve suture (Case 2).

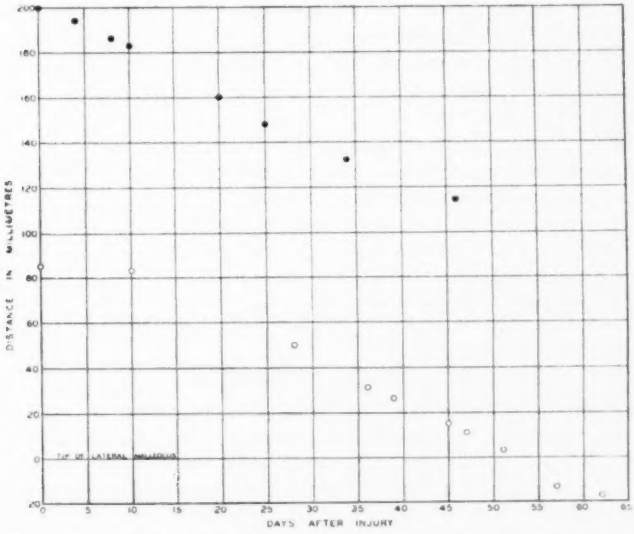


CHART 2.—Advance of Hoffmann-Tinel sign in a case of sural-nerve and musculocutaneous-nerve crush.

CONCLUSIONS AND SUMMARY

An analysis of the data recorded in this and in previous papers justifies the following conclusions:

1. The evidence derived from reliable data based on serial observations indicates that as regeneration proceeds the point at which the Hoffmann-Tinel sign can be elicited moves down the nerve at a progressively diminishing rate. If it is accepted that this sign is evidence of the presence of "young axis-cylinders in the process of regeneration," it may be concluded that regenerating sensory axons (functionally dendrites) proceed distally at a progressively diminishing rate, the rate being higher for the proximal than for the distal part of the limb. This finding demonstrates the importance of making readings over short lengths of the nerve, since these will obviously give the most accurate results. If a mean rate is calculated for the entire nerve, or for long portions of it, the gradual slowing of the regenerative process results in a reduced over-all calculation of the rate. Thus, in Case 1 the rate varied from at least 8.5 mm. a day, in the upper arm, to 2 mm. a day, at the wrist. On the other hand, the mean rate calculated between the lesion and the wrist (exclusive of the delay between injury and the entry of regenerating axons into the distal segment) is 4.6 mm. a day.

2. The findings suggest that over comparable distances of the nerve in the same parts of the limb the rate of advance is slower after suture than after a lesion recovering spontaneously. More observations will be required to confirm whether or not this is correct.

3. The rate varies from one person to another, but in any particular subject it will always be greater in the proximal than in the distal part of the limb.

4. In lesions recovering spontaneously the rate may be very high indeed in the initial stages. Thus, in Case 1 the initial rate in the proximal part of the limb must have exceeded 8.5 mm. a day.

5. Owing to the proximity of the intact proximal segment, it is difficult to ascertain by the technique used to elicit the Hoffmann-Tinel sign when regenerating axons have crossed the injured zone and therefore to calculate the interval elapsing between the injury and the time when the axons enter the distal segment (initial delay). However, it was possible in cases in which the sign was first elicited from the distal segment a short distance below the site of injury to estimate approximately the delay before regenerating axons crossed the injured segment. In Case 3 the initial delay was approximately two days for the sural nerve and nine days for the musculocutaneous nerve.

6. The rate of descent of the Hoffmann-Tinel sign in the cutaneous nerves in the lower leg appeared to be constant, but in these cases amputation terminated the investigation before the regenerating axons could be followed over a suitably long portion of the nerve. Furthermore, the region studied involved the peripheral part of the nerve, where the rate is slowest and where it approaches a constant value for adjacent lengths. The average rate over the length of nerve studied was approximately 2 mm. a day.

OPTIC ATROPHY CAUSED BY AN ARTERIOVENOUS ANGIOMA

Report of a Case

LIEUTENANT RAYMOND I. BAND
MEDICAL CORPS, ARMY OF THE UNITED STATES

CUSHING and Bailey,[1] in a monograph published in 1928, completely reviewed the literature and contributed their own experiences with tumors arising from blood vessels of the brain. Dandy [2] in the same year contributed two papers on the same subject. Thus, this subject was clarified and a solid base was formed for further work.

Cushing and Bailey [1] divided the tumors of cerebral blood vessels into two groups: (1) the angiomatous malformations and (2) the hemangioblastomas, or true neoplasms of blood-vessel elements. The malformations were further subdivided into (1) telangiectases, chiefly capillary; (2) angioma venosum, chiefly venous, and (3) angioma arteriale, arteriovenous. The angioma venosum group was further subdivided into (*a*) the simple varix; (*b*) the serpentine varix, superficial, and (*c*) the racemose, or cirsoid varix—a congeries of deep-seated vessels. The angioma arteriale was subdivided into the serpentine and the racemose, or cirsoid, type.

Dandy [2a] suggested that the term hemangioma not be used with reference to the malformations. He classified the pathological blood-vessel groups under (1) venous, (2) arterial, and (3) arteriovenous categories. He subdivided the arteriovenous group into (*a*) those with direct arteriovenous connection, and (*b*) those with arteriovenous connection through an intermediate mass of abnormal vessels, taking the place of the usual capillary bed. The latter group is similar to the angioma arteriale of Cushing and Bailey. In a later article,[2b] Dandy referred to a venous malformation as an angioma plexiforme. Dandy used the term angioma both for true tumors and the cavernous type of malformation. Both Dandy and Cushing and Bailey based their explanation of the formation of these anomalies on Streeter's [3] work. The blood supply of the brain is developed from a general capillary network which undergoes many changes; these developmental changes would allow not only for much variation but also for the aforementioned malformations if the development

From the Neurology Section, Neuropsychiatric Service, Valley Forge Army Hospital, United States Army, Phoenixville, Pa.

1. Cushing, H., and Bailey, P.: Tumors Arising from Blood Vessels of the Brain, Springfield, Ill., Charles C Thomas, Publisher, 1928.

2. Dandy, W. E.: (*a*) Arteriovenous Aneurysm of the Brain, Arch. Surg. **17**:190-243 (Feb.) 1928; (*b*) Venous Abnormalities and Angiomas of the Brain, ibid. **17**:715-793 (May) 1928.

3. Streeter, G. L.: The Development Alterations in the Vascular System of the Brain of the Human Embryo, Contrib. Embryol. **8**:5-38, 1918.

went awry. As is pointed out, the type of malformation would depend on the stage of development at which the vessels stopped following the usual course.

The primarily venous lesions consist of simple varices or complex entwined masses of veins. The arteriovenous lesions consist usually of an abnormally large artery, or group of arteries, emptying through a mass of abnormal vessels into large veins.

Bergstrand, Olivecrona, and Tönnis [4] classified these angiomatous malformations into two basic groups, as originally brought out by Cushing and Bailey. These groups were differentiated by the presence or absence of parenchyma between the elements of the malformation. Angioma cavernosum does not have parenchyma between its elements, whereas angioma racemosum does. Angioma racemosum is further subdivided as follows: (1) telangiectasia and (2) Sturge-Weber disease, both well-defined anatomic and clinical entities made up of capillary or precapillary vessels; (3) angioma racemosum arteriale; (4) angioma racemosum, venosum, and (5) aneurysma arteriovenosum. The pure arterial type in cases reported is in reality the arteriovenous type.

The commonest of these angiomatous malformations is the aneurysma arteriovenosum. According to Olivecrona and Riives,[5] the vessels interposed between the arteries and the veins in angioma racemosum may have anatomic characteristics of arteries or veins, but most of the vessels are undifferentiated and are of pathological structure.

Since the advent of carotid angiography, the frequency with which these lesions are diagnosed, according to Olivecrona and Riives, is seven times that reported by Cushing and Bailey [1] and Dandy.[2] The malformations occur more frequently in males. They usually give rise to symptoms in the second or third decade of life, though there is great variability as to the age of onset. These malformations are located, in order of frequency, along the course of the middle cerebral artery, next, along the anterior cerebral artery, then, in an area to which the anterior and middle cerebral arteries contribute equally, and, least frequently, along the vertebral artery. The symptom most frequently encountered is epileptic seizure. Subarachnoid hemorrhage, hemiplegia, bruits, papilledema, and signs of increased intracranial pressure, described in the early cases, are not symptoms frequently mentioned in Olivecrona's [5] and Norlén's [6] series of cases.

In reviewing the literature, I have found no cases which presented the symptom of blindness and the lesion of optic nerve atrophy only.

In one of Dandy's [2b] cases ocular neuralgia, bitemporal hemianopsia, bilateral temporal pallor of primary optic atrophy, destruction of the posterior clinoid processes, and a deep sella turcica were present. Operation showed a bluish tumor protruding anteriorly between the optic nerves. After exposure, a mass of entwined veins was revealed. There were no pulsations, nor was there any evidence of arterial blood. Dandy concluded that this tumor was a venous anomaly and termed it angioma plexiforme.

4. Bergstrand, H.: Olivecrona, H., and Tönnis, W.: Gefässmissbildungen und Gefässgeschwülste des Gehirns, Leipzig, Georg Thieme, 1936.

5. Olivecrona, H., and Riives, J.: Arteriovenous Aneurysms of the Brain: Their Diagnosis and Treatment, Arch. Neurol. & Psychiat. **59**:567-602 (May) 1948.

6. Norlén, G.: Arteriovenous Aneurysms of the Brain, J. Neurosurg. **6**:475-549 (Nov.) 1949.

Brock and Dyke [7] correlated the clinical and roentgenographic findings in eight cases of arteriovenous angioma. They reported the case of a young man with a history of "acute epidemic encephalitis" six years prior to their examination. He presented exophthalmos, blindness of the right eye, ocular paralyses, mimetic weakness of the left side of the face, cerebellar signs, and mental deterioration. A large angioma of the right side of the face and a venous angioma of the right retina were present. Roentgenograms of the skull showed two unusually large vascular channels in the right frontal bone, with the channel of the right middle meningeal artery disappearing anteriorly into these channels.

Gross examination of the brain showed an angiomatous mass covering the right optic nerve and the right part of the optic chiasm. Section of the brain revealed bilateral internal hydrocephalus. The angioma extended from the retina and the optic nerve, chiasm, and tract on the right side to the right side of the midbrain and, via the right superior cerebellar peduncle, to the right half of the cerebellum. The mass was diagnosed microscopically as a venous angioma. This case was also reported by Krug and Samuels.[8]

While these two cases are somewhat similar to the case to be reported, a suprasellar-tumor syndrome was present in Dandy's case and a neurocutaneous syndrome with a multiplicity of symptoms referable to the central nervous system was present in Brock and Dyke's case.

I should like to report a case in which optic-nerve atrophy and blindness were the only clinical signs.

REPORT OF CASE

T. C., a white man aged 21, was born in Kentucky in 1930 and lived there until he entered the Army, in January, 1949. He denied having had any but the usual illnesses of childhood. He gave no history of familial disease. He had had no contact with industrial poisons and had had no tropical diseases except malaria. Until November, 1950, he considered himself entirely well.

The patient was stationed in the United States from his enlistment until July, 1950, when he was transferred to Korea. In November, 1950, he first noticed difficulty in seeing. His eyes began to water. He had dull, intermittent frontal headaches, located over both eyes. These headaches were not associated with activity or with any specific time. Acetylsalicylic acid did not relieve the headaches, but they disappeared spontaneously after a month or so and did not return. At this time the patient noted that the vision in his left eye was impaired. Over a period of three months the vision in this eye became progressively poorer. He finally reported to an air station and was hospitalized at the 279th General Hospital. At this time he had no perception in his left eye. Vision in the right eye was normal. The light reflex was not elicited on the left, and the direct pupillary response to light was not obtained on this side. The consensual light reflex was present. On the right, the direct light reflex was present, and the consensual reflex was absent. The left optic disk appeared atrophic, and the right disk appeared paler than normal. Examination otherwise revealed nothing abnormal.

The patient was then transferred to the Zone of the Interior, and then to Valley Forge General Hospital on March 20, 1951. At this time the findings were about the same. The left optic disk was white and avascular; the right disk was pale. The left eye was completely blind. The right eye showed a normal visual field and visual acuity of 20/20 with ability to read Jaeger type 1. These findings have remained the same to the time of this report. Complete blood studies, urinalysis, and spinal-fluid studies revealed nothing abnormal. Roentgenograms of the chest, skull, and orbits all showed a normal condition. A pneumoencephalogram, obtained on

7. Brock, S., and Dyke, C. G.: Venous and Arterio-Venous Angiomas of the Brain: Clinical and Roentgenographic Study of 8 Cases, Bull. Neurol. Inst. New York **1**:247-293 (July) 1932.

8. Krug, E. F., and Samuels, B.: Venous Angioma of the Retina, Optic Nerve, Chiasm and Brain, Arch. Ophth. **8**:871-879 (Dec.) 1932.

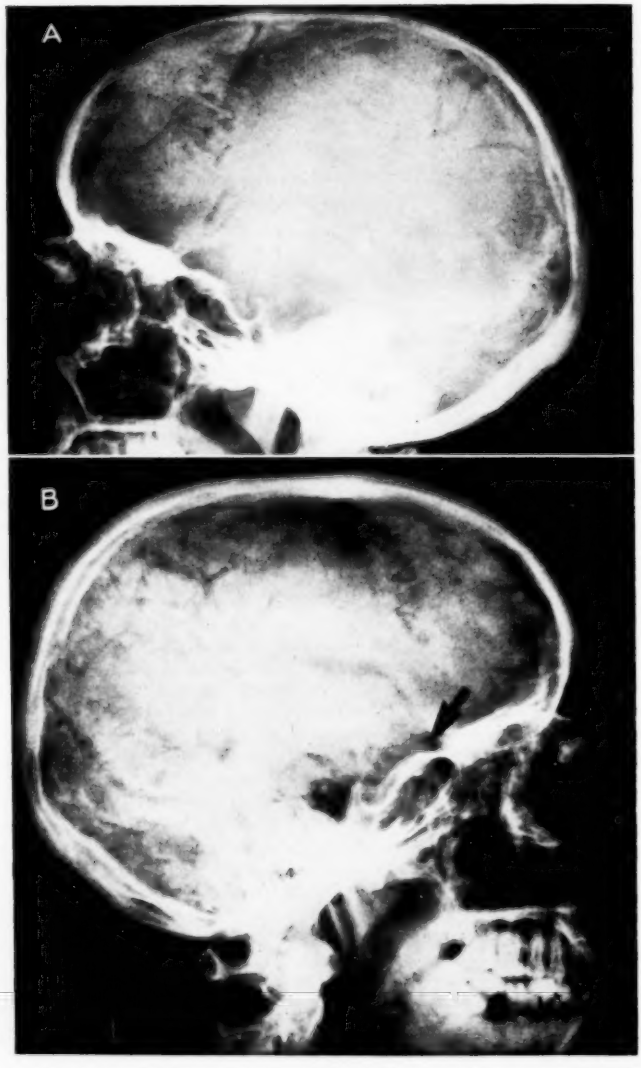


Fig. 1.—*A*, roentgenogram of the skull, showing no abnormalities. *B*, pneumoencephalogram, showing incomplete filling of the optic cistern.

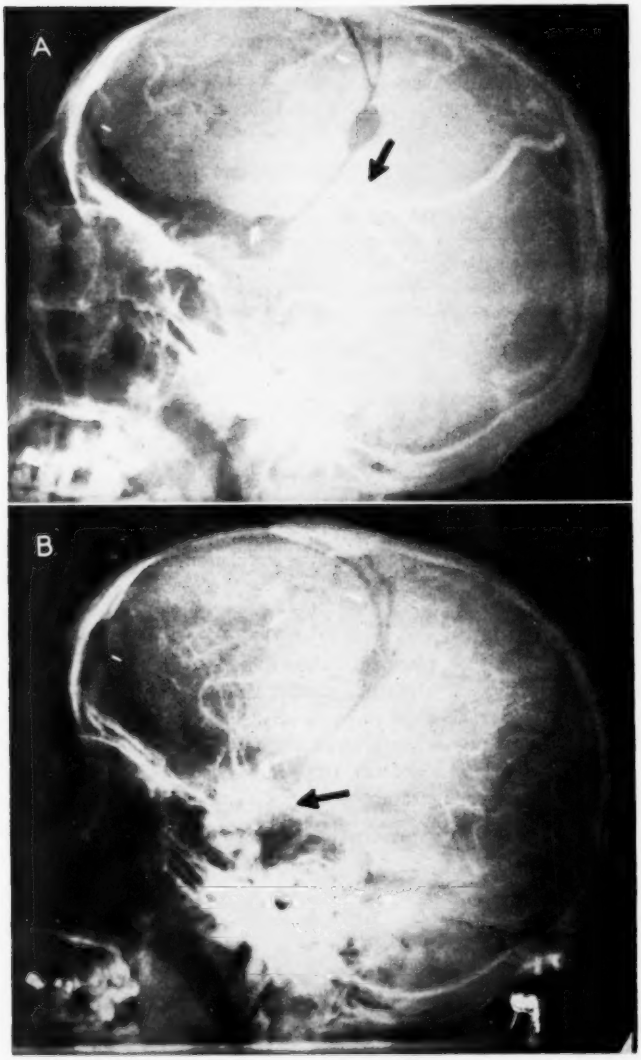


Fig. 2.—*A*, arteriogram, showing abnormal mass of vessels in the region of the optic chiasm. *B*, venogram, showing abnormal cortical vessels emptying into the superior sagittal sinus.

May 8, showed fair filling of the ventricular system and subarachnoid spaces. The basal cisterns failed to show any definite abnormality, although it was thought that the chiasmatic cistern did not fill completely.

On July 10, a flap was turned in the right frontotemporal region. The frontal lobe was retracted. In the region of the chiasm and below it, in the suprasellar region, a nest of vessels, somewhat like a bag of worms, and measuring 1 by 2 cm., was seen. These vessels appeared to be 4 to 5 mm. in diameter. They did not pulsate but appeared thicker and redder than veins. Several of the large vessels surrounded the right optic nerve, and one large vessel ran across the medial aspect of the left optic nerve. No definite major vessels could be seen entering the mass. The operation was ended with the exploration. The patient made an uneventful recovery.

Aug. 27, an arteriogram was made of the right internal carotid system. Good filling of the arterial tree was obtained. A plexus of abnormal blood vessels in the supraclinoid region was visualized in the arterial film. The point of origin of these vessels was not visualized. The branches of the anterior and middle cerebral arteries were filled and showed no definite abnormality. These arteries appeared to be smaller than normal. A venogram failed to reveal dye in the area of the abnormal plexus of vessels. There was good filling of the superior sagittal sinus. There was also filling of an abnormal vessel, probably a cortical vessel emptying into the superior sagittal sinus.

Because of the rapid filling of this angioma during the arteriographic procedure, and because of the reddish color of the blood seen at operation, the lesion was thought to be an arteriovenous angioma. No vessels of origin feeding this mass of vessels could easily be uncovered, and it was believed by the neurosurgeon, Major W. H. Kimsey, that further manipulation in this inaccessible area was not advisable.

Olivecrona and Riives [5] and Norlén [6] have pointed the way to the surgical treatment of certain of these lesions. Norlén has demonstrated by angiography that the cerebral circulation in the presence of these angiomas is impaired. He has shown that after removal of the lesion the rest of the circulation returns to normal.

SUMMARY

A case of bilateral optic nerve atrophy and blindness of the left eye without any other signs or symptoms is presented. The cause, as determined at operation and by carotid angiography, was a vascular malformation in the supraclinoid region at the optic chiasm. This malformation could be included in the category of angioma racemosum, aneurysma arteriovenosum, of Bergstrand, Olivecrona and Tönnis.

The literature is reviewed and two somewhat similar cases are presented. No other case was found in the literature with optic nerve atrophy and blindness as the only presenting signs.

CLINICAL AND ELECTROENCEPHALOGRAPHIC EFFECTS OF PREFRONTAL LOBOTOMY AND TOPECTOMY IN CHRONIC PSYCHOSES

ERICH G. KRUEGER, M.D.
AND
HENRIETTE LOEWENBERG WAYNE, M.D., Sc.D.
NEW YORK

THIS REPORT deals with clinical and electroencephalographic observations on, and is a part of a comparative study of, the effects of prefrontal lobotomy and topectomy in a group of 105 patients with chronic psychoses who were admitted to the Veterans Administration Hospital, Bronx, New York, for psychosurgical procedures over a period from March, 1947, to December, 1950.

CLINICAL OBSERVATIONS

Case Material and Procedures.—With the exception of one patient with manic-depressive psychosis, all had chronic advanced schizophrenia of paranoid, hebephrenic, or catatonic type. A comparative study of the effects of prefrontal lobotomy and topectomy seemed to be particularly applicable in a rather homogeneous group of patients with advanced schizophrenia. A selection of the patients for one or the other procedure was deliberately avoided. All 105 patients—84 from the Northport Veterans Administration Hospital, 17 from the Canandaigua Veterans Administration Hospital, and four from other hospitals—were selected for psychosurgical procedures by the lobotomy boards of the various hospitals, according to several criteria. The duration of illness was at least two or three years, with an average duration of five years. All patients had had previous treatment, consisting of institutional care, electric shock, or insulin coma, resulting in little or no improvement. Most patients came from the wards for disturbed patients and constituted grave problems in management. Their symptoms ranged from violent, destructive, assaultive, homicidal, suicidal, or agitated behavior to apathy, complete withdrawal, and marked deterioration, with lack of control of bodily functions. Several patients had required prolonged tube feeding, and many had been under continuous medical sedation or pack therapy for a long period. The prognosis was considered extremely poor in all cases. The majority of the patients, mostly of similar social background, were young to middle-aged male veterans of World War II, with an average age of approximately 30. After transfer to the Bronx Veterans Administration Hospital, the patients were reevaluated for the advisability of psychosurgery after a preoperative observation period of two to four weeks, during which time various laboratory procedures and psychological tests were per-

From the Neurosurgical Section, Veterans Hospital, Bronx, N. Y. (Dr. Krueger).

From the Neuropsychiatric Service, Veterans Administration Hospital, Bronx, N. Y. (Dr. Wayne).

Financial Publication Assistance Provided by Ad Men's Post No. 209, American Legion, New York.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

formed. Many of the patients were too disturbed to permit psychological studies, and in some instances other laboratory procedures. After operation, the patient remained for an observation period ranging from one to three months before transfer to the referring hospitals for further observation and reintegrative treatment.

Twenty patients were subjected to a standard type of bifrontal topectomy involving Areas 9 and 10, and part of Area 46, according to the technique originally used by the Columbia-Greystone Associates.[1] The bilateral, rectangular parasagittal block excisions were made 1 cm. above the orbital pole, extending 5 cm. upward in anteroposterior direction along the dorsal surface of the frontal lobe, and measuring 5 cm. in width and 1.9 cm. in depth. In the 87 prefrontal lobotomies an open type of procedure, allowing direct vision, was used, as described by Scarff and Kalinowsky.[2]

One of the 20 patients subjected to topectomy died on the eighth postoperative day. Reexploration on the seventh postoperative day failed to disclose a suspected hematoma. Cerebral edema was assumed to be the probable cause of death. Permission for autopsy could not be obtained. There was no fatality in 86 lobotomies, 2 of which were carried out on patients who failed to show any improvement after topectomy.

Wound infections, with the later development of osteomyelitis of the bone button, or of the bone flap, occurred in one patient of the lobotomy group and in one of the topectomy group. The latter patient remained severely disturbed after operation, removing his dressing and soiling his wound on several occasions. Later, he showed no change in his mental status as a result of topectomy and after a subsequent operation with general anesthesia for removal of the ostomyelitic bone flap. However, he responded well to lobotomy 11 months after topectomy.

Clinical Results.—In assessing the clinical improvement, we were partially dependent on observations and follow-up reports obtained from the various referring hospitals. However, for the sake of a more uniform evaluation, and in order to have a sufficiently long follow-up interval, we limited the clinical evaluation, but not the electroencephalographic studies, to those schizophrenic patients admitted from the Northport Veterans Administration Hospital during the year 1947-1948, with the exception of four patients of the topectomy group. Sixty-two of these patients were lobotomized during 1947-1948, including 11 patients not operated on in the Bronx Veterans Administration Hospital. The topectomies were carried out between August, 1948, and October, 1949. As of March, 1951, the postoperative follow-up period was approximately 2 to 4 years in the lobotomy group and 2 years 7 months to 1½ years in the topectomy series.

The clinical results in the lobotomy group of 62 schizophrenic patients were previously reported in detail by Drubin in a preliminary study [3] and a later follow-up report.[4] On the basis of Drubin's classification of improvement, the patients were divided into four groups: (1) patients with marked improvement, including those who adjusted well after discharge, on trial visit, or on ground privileges in the hospital; (2) patients with moderate improvement, including those with fair to marginal adjustment on discharge, trial visit, ground privileges, or assignment to

1. Mettler, F. A., Editor, Selective Partial Ablation of the Frontal Cortex: A Correlative Study on Its Effect on Human Psychotic Subjects, by the Columbia-Greystone Associates, New York, Paul B. Hoeber, Inc., 1949.

2. Scarff, J. E., and Kalinowsky, L. B.: Prefrontal Lobotomy Under Direct Vision, New York J. Med. **47**:2669-2675, 1947.

3. Drubin, L.: Preliminary Report of 62 Prefrontal Lobotomies on Psychotic Male Veterans at the Veterans Hospital, Northport, Long Island, New York, J. Nerv. & Ment. Dis. **112**:301-310, 1950.

4. Drubin, L.: Further Observations on 62 Lobotomized Psychotic Male Veterans at the Veterans Hospital, Northport, New York, J. Nerv. & Ment. Dis. **113**:247-256, 1951.

better wards; (3) patients with slight improvement, including those who showed improvement in their previous mental condition, with better adjustment to the same or a better type of ward, and (4) patients showing no improvement.

In the lobotomy group of 62 patients, 17 (27%) showed marked improvement; 19 (31%), moderate improvement; 17 (27%), only slight improvement, and 9 (15%), no improvement. Twenty-two patients (35%) have been able to remain outside the hospital. No patient was considered cured or as having a complete remission.

Of the 19 schizophrenic patients—12 of the paranoid, 4 of the catatonic, and 3 of the hebephrenic reaction type—who were subjected to topectomy, 3 (16%) showed moderate improvement, with ground privileges in the hospital. Four patients (22%) showed only slight improvement, whereas 12 (62%) were unimproved and continued to present serious problems in management. Some of these 12 patients had shown initial improvement but soon relapsed to their original status. None of the patients were discharged from the hospital; none could be classified as greatly improved at the time of evaluation. A more detailed report of our results following topectomy will be the subject of another paper.

Lobotomy after ineffectual topectomy was carried out on seven of the patients who showed no improvement—three from the Canandaigua Veterans Administration Hospital, two from the Northport Veterans Administration Hospital, and two from the Bronx Veterans Administration Hospital—at intervals of 4, 10, 10, 11, 14, 15, and 22 months, respectively, after topectomy. One of these patients was discharged with marked improvement; two are on parole to visit their families; one is on ground privileges, and three are slightly improved and have been admitted to a better ward.

Comment.—Assessment of the results of topectomy as compared with those of lobotomy showed that the rate of clinical improvement following topectomy fell considerably below that following lobotomy. Appreciable improvement (Groups 1 and 2) was noted in 58% of the lobotomy series but moderate improvement in only 16% of the topectomy series. Lobotomy after ineffectual topectomy in seven patients resulted in marked to moderate improvement in three patients and in slight improvement in the remaining four patients. The latter observation is of interest, since Pool [5] claimed that lobotomy after topectomy did not achieve further improvement. The discrepancy in the length of the follow-up period in the two series did not appear to be significant, since the results in the lobotomy series were even more favorable at an interval comparable to the present follow-up period in the topectomy group. The numerical inequality of the two series could be used as a critical argument. On the other hand, the good results reported by Heath and Pool [6] in the original series of schizophrenic patients subjected to topectomy involving Areas 9, 10, and 46 were obtained in a group of approximately equal size. It is therefore reasonable to assume that the difference between the results in our series of topectomies and the results of the Greystone Associates and those of our lobotomy group is based on the greater severity and chronicity of the psychopathologic process in our case material.

5. Pool, J. L.: Topectomy, 1946-1951: Report on 106 Consecutive Nonproject Topectomy Operations, Tr. & Stud. Coll. Physicians, Philadelphia **19**:49-67 (Aug.) 1951.

6. Heath, R. G., and Pool, J. L.: Bilateral Fractional Resection of Frontal Cortex for the Treatment of Psychoses, J. Nerv. & Ment. Dis. **107**:411-429, 1948. Mettler.[1]

Similar observations were made by several groups of workers who carried out partial lobotomies or fractional isolation of the prefrontal cortex. Egan,[7] who isolated the orbital quadrants in 53 patients by horizontal and vertical cuts, reported that the results were inferior as compared with those in a standard lobotomy series. Meyer and Beck,[8] in a neuropathological study, demonstrated that incomplete severance of thalamofrontal projections in different planes achieved equally good clinical improvement. Repeated, more complete lobotomy would produce satisfactory results in some instances in which a previous partial lobotomy had failed to do so. In a recent report on the results of selective cortical undercutting, Scoville, Wilk, and Pepe [9] observed a considerably lower rate of improvement in a series of schizophrenic patients in one state hospital than in another hospital, where "the dregs of the disturbed wards had already undergone psychosurgery."

The experiences of Scoville, Wilk, and Pepe, furthermore, appear to contradict the assumption of therapeutic specificity ascribed to certain areas of the prefrontal cortex, since these authors obtained equally good clinical improvement with undercutting of orbital, superior frontal, or cingulate gyri. Other observations, particularly the clinicoanatomical studies of Meyer and Beck,[8] as well as those of Meyer and McLardy,[10] based on leucotomy material, and, we believe, our observations, are likewise in support of a quantitative principle which underlies the mechanism on which the clinical improvement following psychosurgery may be based. However, we do not intend to convey the impression that partial lobotomy, fractional isolation, or excision of areas of the prefrontal cortex is generally ineffectual in patients with chronic schizophrenia. On the contrary, the evidence accumulating in the literature strongly indicates that good clinical results, with reduction of undesirable side-effects, can be obtained by less radical procedures, such as partial lobotomy, topectomy, or selective cortical undercutting. On the other hand, a standard lobotomy may be necessary, preferably perhaps as a secondary procedure, in instances in which the psychopathological process has advanced beyond a certain degree of chronicity and severity.

ELECTROENCEPHALOGRAPHIC OBSERVATIONS

Electroencephalographic studies were carried out on 96 of 105 patients admitted for psychosurgical procedures. In 3 of 96 patients the test results were unsatisfactory because of the patients' inability to cooperate properly. Twenty patients of this group had only one recording, either preoperative or postoperative, largely because in 1947 and early in 1948 sleep records were not carried out on patients who were too disturbed to be tested while they were awake.

Preoperative Results.—Approximately 50% of the 96 patients tested had sleep studies prior to and after operation, and in many instances this was the only reliable

7. Egan, G.: Results of Isolation of the Orbital Lobes in Leucotomy, J. Ment. Sc. **95**:115-123, 1949.

8. Meyer, A., and Beck, E.: Neuropathological Problems Arising from Prefrontal Leucotomy, J. Ment. Sc. **91**:411-425, 1945.

9. Scoville, W. B.; Wilk, E. K., and Pepe, A. J.: Selective Cortical Undercutting, Am. J. Psychiat. **107**:730-738, 1951.

10. Meyer, A., and McLardy, T.: Clinico-Anatomical Studies of Frontal Lobe Function Based on Leucotomy Material, J. Ment. Sc. **95**:403-417, 1949.

means of testing an uncooperative patient. In 45 patients sleep was induced by intravenous administration of amobarbital sodium (amytal sodium®) about half an hour before the test. Chloral hydrate was administered to only three patients. The latter seemed to be more practical for patients who tended to become agitated and fearful with amobarbital sodium.

The majority of our patients had normal preoperative records. Only 15 patients had abnormal tracings—12 with nonfocal, mildly paroxysmal waves of 3- to 7-cps frequency and 3 with focal paroxysmal activity. In one patient the foci were located in the right anterior temporal area toward the frontal lobe; in another, in the left anterior temporal area, and in a third, in the frontal region bilaterally.

The recorded number of moderate, nonspecific abnormalities did not exceed that seen in a normal (control) group. Patients with paroxysmal pathological records and with focal lesions were reevaluated clinically and by means of air studies prior to operation. Consideration was also given to the fact that all these patients had previously undergone extensive electric and insulin shock therapy. Although abnormalities are regarded as largely reversible in 6 to 12 weeks after completion of shock treatment, occasional residual dysrhythmias and cerebral damage have been reported in the literature.[11] In fact, the history of the patient with the focus in the left temporal lobe suggests the possibility of localized head trauma during or after shock treatment (Fig. 1). In this group there were also two patients who had been prize fighters prior to their illness and may have suffered cerebral trauma.

Postoperative Results.—Postoperative waking records were obtained on about half the patients, and about two-thirds underwent sleep studies, made either exclusively or combined with waking records. For all patients of this group we have, however, compatible tracings prior to and after operation. In some patients we also recorded spontaneous sleep activity. All patients were retested between the 10th and the 35th day after operation.

On the whole, the patients who underwent topectomy had less severe defects than the patients who were lobotomized. Only one patient in either group had borderline records, with very slight changes up to the time of their transfer to the hospital from which they had been referred. However, reports indicate that this number of normal tracings has increased to 15 as of the end of 1950.[12] All other patients, subjected to lobotomy or topectomy, had more or less abnormal tracings shortly after operation, a finding in keeping with that of other investigators.[13] Most patients had slow-wave activity of 1- to 3-cps frequency in the frontal area, which is a characteristic finding in the early postoperative stage. Others showed a marked sway in the base line. Thirty-six patients had diffusely abnormal records with slow,

11. Bagchi, B. K.; Howell, R. W., and Schmale, M. T.: Electroencephalographic and Clinical Effects of Electrically Induced Convulsions in Treatment of Mental Disorders, Am. J. Psychiat. **102**:49-60, 1945. Barrera, S. E., and Pacella, B. L.: Electroencephalographic Findings Associated with Electric Shock Therapy in Patients with Mental Disorders, Am. J. Physiol. **133**:206, 1941.

12. Drubin, footnotes 3 and 4.

13. (*a*) Cohn, R.: Electroencephalographic Study of Prefrontal Lobotomies, Arch. Neurol. & Psychiat. **53**:283-288 (April) 1945. (*b*) Hutton, E. L.; Flemming, G. W. T. H., and Fox, F. E.: Early Results of Prefrontal Leucotomy, Lancet **2**:3-7, 1941. (*c*) Greenblatt, M.: The Electroencephalogram: Pre- and Post-Lobotomy, J. Nerv. & Ment. Dis. **109**:269, 1949.

2- to 5-cps frequencies, or generally disorganized tracings, which were often associated with a greater slow-wave abnormality from the frontal area.

Eight lobotomy patients showed seizure discharges in their records two to four weeks after operation, only three of whom had clinical seizures early after operation and prior to testing, while the remaining five patients, who had shown paroxysmal tendencies in their postoperative electroencephalograms, had not exhibited clinical seizures up to the end of 1950.[12] Two patients who had one postoperative seizure showed no paroxysmal activity when they were tested subsequently. At that time, however, these patients had received anticonvulsant medication, which may have controlled their seizure discharges. Findings such as these should not lull the physician, but, rather, should make him alert to observe carefully postlobotomy patients for increasing seizure activity by serial electroencephalograms, and, if this develops, to institute anticonvulsant therapy before clinical seizures occur.

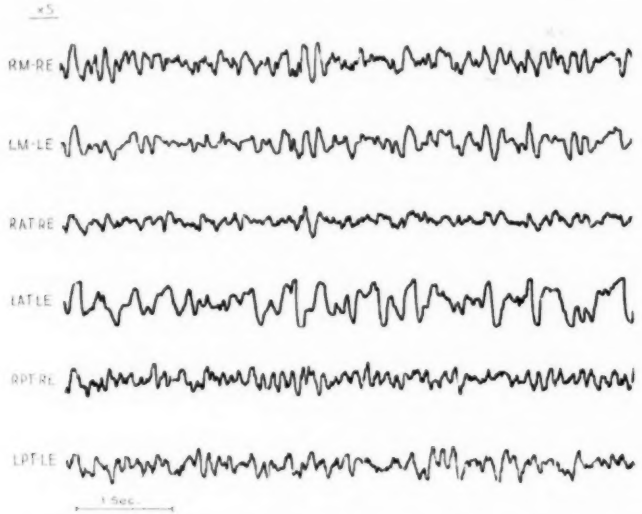


Fig. 1.—Prelobotomy electroencephalogram for W. H., aged 21, with schizophrenia, paranoid type, showing paroxysmal slow-wave-and-spike-seizure focus in the left anterior temporal area.

From the follow-up reports so far at our disposal, it may fairly be estimated that about 30% of our lobotomized patients have meanwhile had one or recurrent clinical seizures, which were, on the whole, fairly well controlled by anticonvulsant medication.

Follow-up reports on 19 topectomized patients indicate that 8 (42%) had clinical grand mal seizures up to 12 months after operation. Six of these patients did not show evidence of seizure discharges or clinical seizure activity at the time of their transfer from this hospital, one month to six weeks after operation. In one patient who underwent a lobotomy and in one who underwent topectomy and subsequent lobotomy clinical seizure activity developed concomitant with osteomyelitis of the skull, which required further surgical intervention.

The incidence of clinical seizures in our lobotomy group, as well as in our topectomy group, is higher than that of most observers.[14] Several factors may account for this result. First, we included every patient who exhibited seizures at any time after the operation. In some statistics,[15] seizures which occurred in the first postoperative week were not included or were listed separately, because it was assumed that they were due to cortical swelling or to some other immediate postoperative sequela, rather than to a true convulsive disorder. Another reason may be the length of the follow-up period in our series, which extended over three years for about half our patients. In our lobotomy group, the incidence of seizures did not exceed 12% after the first year, which is in accordance with that of most investigators.[16] The operative technique of open lobotomy, which involves a wider exposure of the prefrontal area and placement of the trephine areas closer to the midline, varying in this respect from the Freeman-Watts procedure, may be another

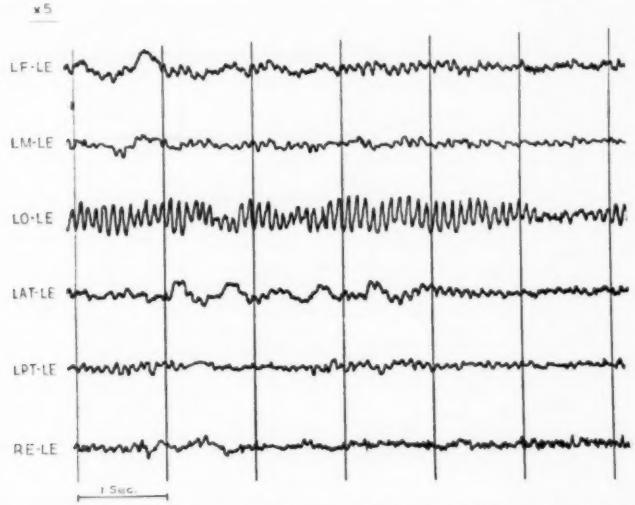


Fig. 2.—Electroencephalogram for H. S. C., aged 24, with schizophrenia, mixed type. The preoperative tracing was normal. The postoperative record, taken 13 days after topectomy, shows a slow-wave focus in the left anterior temporal area. There is much less slowing in the left frontal region in comparison.

14. Prefrontal Lobotomy in 1,000 Cases, Board of Control, England and Wales, London, His Majesty's Stationery Office, 1947. Cohn.[13a] Pool, J. L.; Heath, R. G., and Weber, J. J.: Topectomy: Surgical Indications and Results, Bull. New York Acad. Med. **25**:335-344, 1949. Scoville, W. B.: Selective Cortical Undercutting as a Means of Modifying and Studying Frontal Lobe Function in Man, J. Neurosurg. **6**:65-73, 1949.

15. Mettler.[1] Scoville, Wilk, and Pepe.[9]

16. Freeman, W., and Watts, J.: Prefrontal Lobotomy: Study of 331 Cases, Am. J. M. Sc. **211**:1-8, 1946. Bennett, A. E.; Keegan, J. J., and Wilbur, C. B.: Prefrontal Lobotomy in Chronic Schizophrenia, J. A. M. A. **123**:809-813 (Nov. 27) 1943. Cohn.[13a] Levin, S.; Greenblatt, M.; Healy, M. M., and Solomon, H. C.: Electroencephalographic Effects of Bilateral Prefrontal Lobotomy: Comparison of Cases With and Without Post-Lobotomy Seizures, Am. J. Psychiat. **106**:174-184, 1949.

vital factor. Only Stevens and Mosovich [17] reported a high rate (33.3%) of postoperative convulsions in their lobotomy series. These authors were not able fully to account for this incidence, but they considered the following possible factors: (1) the closer scrutiny and observation of patients who remained permanently institutionalized during the follow-up period; (2) their late follow-up reports, which list the first appearance of seizures as late as 25 months after operation; (3) the lower convulsive threshold, due to extensive shock therapy prior to the operation; (4) dying cortical cells and secondary progressive atrophy of the frontal cortex.

However, the incidence of seizures was also much higher in our topectomy group than in Pool's experience. Although we employed a similar operative approach, he observed a seizure incidence of only 16% in 100 topectomies.[5]

An electroencephalographic finding thus far unexplained, observed mainly in topectomized patients, is a pronounced involvement of the anterior temporal area.

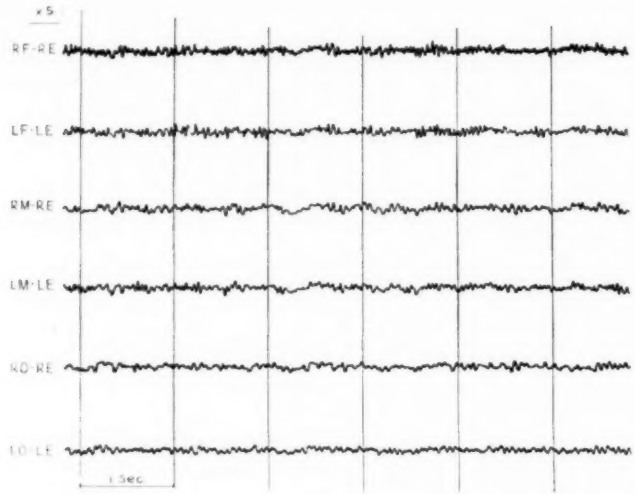


Fig. 3.—Preoperative (normal) electroencephalogram of W. A., aged 29, with schizophrenia, taken one-half hour after intravenous injection of amobarbital sodium, 7½ grains (0.5 gm.), showing mildly drowsy patterns and a fair amount of 18- to 24-cps. frequencies (barbiturate effect).

This abnormality consists of irregular, slow-wave activity, which may vary from 2 to 5 cps in frequency. In some instances this defect of the temporal lobe was much severer than that of the frontal area. We are not able to offer any explanation for this involvement of the temporal lobe, since the incision did not go beyond the prefrontal area in any case. It may be assumed that as a result of the operation frontotemporal pathways became involved (Fig. 2).

In many of our postoperative sleep studies, we made the further observation that cortical reaction to barbiturates, particularly to amobarbital sodium, had undergone

17. Stevens, H., and Mosovich, A.: Clinical and Electroencephalographic Investigations of Prefrontal Lobotomy Patients, Am. J. Psychiat. **104**:73-80, 1947.

changes. While normally, or when a patient is aroused after a short period of sleep,[18] the cortex responds with pronounced acceleration of rhythm, varying from 16 to 28 cps in frequency, until a moderately deep sleep is established, many of our postoperative patients, both those who had undergone lobotomy and those who had had topectomy, no longer showed this pattern. The fast frequencies were either abolished or greatly reduced, particularly in the frontal area. Since our patients returned to other Veterans Administration hospitals from 6 to 12 weeks after the operation, we have been unable to verify whether this change was transitory or permanent (Figs. 3 and 4). Similar observations, however, were reported by Henry, Darrow, and Boshes[19] in their series of experimental lobotomies.

Another finding observed during sleep was the reduction or absence of 12- and 14-cps sleep spindle activity in most of our postoperative patients. Ten patients showed neither 12- nor 14-cps sleep spindles in their records; 5 patients had 14-cps

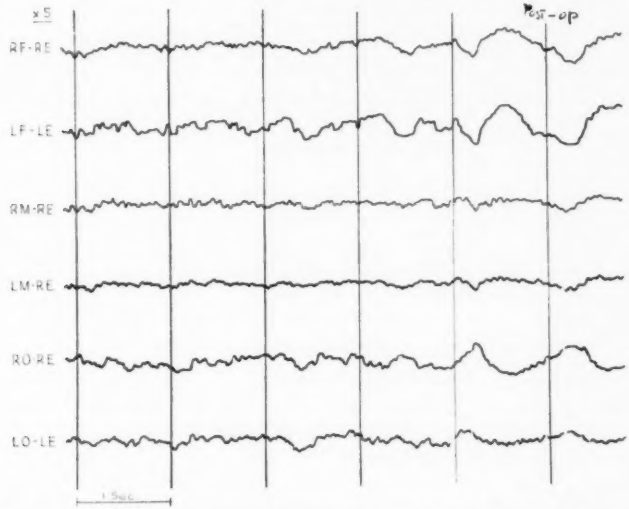


Fig. 4.—Post-topectomy electroencephalogram for W. A., aged 29, with schizophrenia, taken on the 27th day after topectomy and one-half hour after intravenous injection of amobarbital sodium, 7½ grains (0.5 gm.), showing pathological tracings in a very drowsy patient. Maximal slowing is seen in the left frontal region. A barbiturate effect was not elicited at any time.

sleep spindle formation, but the remaining patients showed spindles only in an aborted form, if at all. Lennox and her associates, and Murphy had reported conflicting results in this respect in their series of lobotomies.[20] While in our loboto-

18. Brazier, M., and Finesinger, J. E.: Action of Barbiturates on the Cerebral Cortex: Electroencephalographic Studies, Arch. Neurol. & Psychiat. **53**:51-58 (Jan.) 1945. Cohn, R., and Katzenelbogen, S.: Electroencephalographic Changes Induced by Intravenous Sodium Amytal, Proc. Soc. Exper. Biol. & Med. **49**:560-563, 1942.

19. Henry, C. E.; Darrow, W., and Boshes, L. D.: Psychological Effects of Prefrontal Lobotomy, Am. Psychologist **3**:360, 1948.

20. Lennox, M., and Coolidge, J.: Electroencephalographic Changes After Prefrontal Lobotomy, with Particular Reference to Effect of Lobotomy on Sleep Spindles, Arch. Neurol. & Psychiat. **62**:150-161 (Aug.) 1949. Murphy, J. P.: Electroencephalography in Lobotomy, Digest Neurol. & Psychiat. **17**:419, 1949.

mized patients sleep spindle activity was absent, except for five patients, as mentioned above, sleep spindles were seen, at least in an abortive form, in all our patients with topectomy. Twelve-per-second sleep spindle activity seemed to be better preserved than the 14-cps spindle activity in our patients with topectomies. In this respect, the lobotomized patients differed apparently from the topectomized patients.

We wish to stress again that our electroencephalographic observations were confined to the early postoperative period. It has been reported that gross pathological lesions, particularly frontal foci, largely disappear from the 6th to the 12th postoperative week,[21] and that persistence of abnormal tracings or appearance of paroxysmal patterns, later, suggest the possibility of developing seizures.[22] The early electroencephalographic findings do not have a definite prognostic value and do not reflect the clinical result of the operation. However, serial electroencephalograms taken over a prolonged follow-up period may indicate which patients are likely to have seizures.

SUMMARY AND CONCLUSIONS

The clinical and electroencephalographic observations following topectomy or lobotomy in a group of 105 patients with chronic psychoses are presented. Com-

Electroencephalographic Data

Operation	Total No. Patients	Waking EEG Only: Preoperative and Postoperative	Sleep Studies: 1 EEG Only	Sleep Studies: Preoperative and Postoperative	Preoperative EEG: Normal	Preoperative EEG: Pathological: Focal	Preoperative EEG: Pathological: Diffuse	Postoperative EEG: Borderline	Postoperative EEG: Abnormal	Paroxysmal EEG Shortly After Operation	Clinical Seizure Shortly After Operation	Clinical Seizure as of March, 1951
Lobotomy	71	18	22	31	58	3	10	1	70	8	3	Estimate, 30%
Topectomy	19	2	3	14	17	..	2	1	18	2	2	8 = 42%

parison of the rate of clinical improvement for 62 lobotomies with that for 19 topectomies in patients with chronic advanced schizophrenia showed a considerably lower value for the topectomy group. It is assumed that this discrepancy is based on the greater severity and chronicity of the psychopathologic process in our case material.

Lobotomy after ineffectual topectomy produced significant improvement in three of seven patients.

The theoretical implications of our clinical results are discussed with regard to similar observations in the literature, the evidence supporting a quantitative principle underlying the mechanism on which the clinical improvement following psychosurgery may be based.

The electroencephalograms in the early stage following prefrontal lobotomy and topectomy showed severe cortical damage in the form of either a diffuse or a focal slow-wave abnormality. The defects were severer after lobotomy than after topectomy.

The brain-wave patterns of many patients who underwent lobotomy or topectomy reacted differently to sedatives, particularly barbiturates, than before operation. At

21. Mettler.[1] Cohn.[13a]

22. Cohn.[13a] Stevens and Mosovich.[17]

this time no definite explanation can be given for this observation, and it should be further investigated.

So far, about 30% of our lobotomy patients show proneness to the development of seizures, whereas only one-third of the patients with paroxysmal patterns had clinical seizures at the time of our examination. Eight (42%) of 19 topectomized patients have now had one or more clinical seizures, while only 2 had shown seizure patterns shortly after the operation.

Normal sleep spindle activity is more impaired in patients who have undergone prefrontal lobotomy than in patients who have undergone topectomy.

The difference in the electroencephalographic pattern following lobotomy and that following topectomy is in accordance with the clinical experience that lobotomy constitutes a more radical procedure than topectomy.

Miss Jane Boyle, supervisory technician of the Electroencephalography Laboratory, Veterans Administration Hospital, New York, gave technical assistance in the preparation of the tracings.

REACTIONS OF DOGS WITHOUT NEOCORTEX DURING CYCLES OF ADDICTION TO MORPHINE AND METHADONE

ABRAHAM WIKLER, M.D.
LEXINGTON, KY.

BECAUSE of recent reports dealing with the effects of frontal lobotomy in narcotic addicts,[1] interest has been renewed in the mechanisms underlying the opiate-abstinence syndrome. It has been shown [2] that frontal lobotomy reduces greatly the craving for narcotics in addicted patients but does not alter the physiologic changes which ensue on abrupt and complete withdrawal of opiates, except when this is carried out concomitantly with the operation, when the abstinence changes may be attenuated, possibly because of temporary "diaschisis." Such studies indicate that the integrity of certain thalamofrontal pathways is not essential for the mechanisms underlying the "nonpurposive" features of the opiate-abstinence syndrome, but they cast no light on the problem of whether the genesis of this phenomenon is related to meaningful factors alone, or to nonmeaningful changes in the organism which are produced directly by repeated, regular injections of opiate-like drugs, or to both.

The investigations to be reported here were designed primarily to determine whether the neocortex is essential for the development of the opiate-abstinence syndrome and whether the genesis of this phenomenon is related, in part at least, to nonmeaningful effects of opiate drugs on the central nervous system. To my knowledge, studies of this sort have not been reported in the literature.[3] The investi-

From the National Institute of Mental Health, National Institutes of Health, United States Public Health Service; Research Branch, United States Public Health Service Hospital.

1. Dynes, J. G., and Poppen, J. L.: Lobotomy for Intractable Pain, J. A. M. A. **140**:15 (May 7) 1949. Hamilton, F. E., and Hayes, G. J.: Prefrontal Lobotomy in the Management of Intractable Pain, Arch. Surg. **58**:731 (June) 1949. Koskoff, Y. D.; Dennis, W.; Lazovik, D., and Wheeler, E. T.: Psychologic Effects of Frontal Lobotomy Performed for the Alleviation of Pain, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:723, 1948. Mason, T. H., and Hamby, W. B.: Relief of Morphine Addiction by Prefrontal Lobotomy, J. A. M. A. **136**:1039 (April 17) 1948. Watts, J. W., and Freeman, W.: Frontal Lobotomy in the Treatment of Unbearable Pain, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:288, 1948.

2. Wikler, A.; Pescor, M. J.; Kalbaugh, E. M., and Angelucci, R. J.: Effects of Frontal Lobotomy on the Morphine Abstinence Syndrome in Man: An Experimental Study, to be published.

3. A preliminary report of these studies has been published (Wikler, A.: Recent Progress in Research on the Neurophysiologic Basis of the Morphine Abstinence Syndrome, Am. J. Psychiat. **105**:329, 1948), but preparation of the complete report was delayed until histologic studies could be made on the remaining brains of the last two decorticated dogs in the series (Wikler, A.: Adaptive Behavior in Long-Surviving Dogs Without Neocortex, Arch. Neurol. & Psychiat. **64**:29 [July] 1950).

gations were concerned also with problems relating to analgesic testing methods in animals and to the addiction liability of methadone, one of the newer potent synthetic analgesic agents.

METHODS AND MATERIAL

The effects of single and repeated doses of morphine and methadone, and of abrupt withdrawal of these drugs, were studied in 13 chronic decorticated dogs, but only on the last 2 preparations was it possible to carry out the studies through complete cycles of addiction to these agents. Since the findings in all preparations were essentially the same, the present report will deal only with observations on the last two preparations, one of which (Dog 66) survived 19 months, and the other (Dog 75) 12 months, after completion of decortication.

A detailed report on the operative techniques employed and the results of studies on adaptive behavior in these animals has been published.[4] For present purposes, it is necessary only to point out that in both preparations all of the neocortex and portions of the archicortex had been ablated and that these animals were incapable of developing auditory, visual, or time-"conditioned" responses. After much training, suggestive evidence of tactile conditioning was noted, but this resembled more the phenomenon of spinal facilitation described by Porter and Taylor.[5] Of relevance to the studies on opiate addiction were measurements of rectal temperature, cardiac and respiratory rates, pain-reaction thresholds, spontaneous motor activity ("circling"), and the intensities of behavioral responses to restraint or to nociceptive stimuli.

Pain-reaction thresholds were measured by a modification of the method of Koll and Reffert.[6] Bilateral silver-mercury amalgam fillings were made in the right upper and right lower canine teeth of Dog 66, and in the right and left lower canine teeth of Dog 75. In testing, the pulp nerve of each tooth was stimulated electrically through blunt-pointed steel electrodes mounted on an "alligator" clamp. The electric current was derived from the 60-cycle line source, after passage through a voltage stabilizer and reduction of voltage by means of isolation transformers. Before each stimulation, the tooth resistance between the electrodes was measured with an ohmeter. The pain-reaction threshold was defined as the lowest voltage which elicited a contraction of the skeletal muscle on the ipsilateral side of the lower lip.

Spontaneous motor activity was observed directly, and was also recorded by means of a specially designed circular pen, the walls of which were made of smooth linoleum and the flaps of hardware cloth, covered with removable linoleum pads and a blanket. When placed in this pen, the preparations displayed alternate periods of "circling" along the walls in either direction and periods of rest or sleep. Such circling movements were recorded when desired by mounting the pen on a low fulcrum and connecting the pen to a sylphon, which transmitted its motions through a closed pneumographic ink-writing device. The latter traced on paper, driven by a constant-speed motor, the displacements of the circular pen which were produced by the weight of the animal. From such tracings, measurements were made of spontaneous circling activity during each hour for variable periods, or continuously for several days.

Except after medication, restraint or pinching regularly evoked "sham rage."[4] The intensities of such responses were graded roughly on the basis of subjective estimates by the observers.

Drugs were prepared in aqueous solutions and were administered subcutaneously in doses of 2 to 10 mg. of morphine sulfate and 2 to 5 mg of methadone hydrochloride, per kilogram of body weight. Observations were made at intervals up to eight hours after injection of the drug, or until evidence of maximal effects were obtained.

4. Wikler, A.: Adaptive Behavior in Long-Surviving Dogs Without Neocortex, Arch. Neurol. & Psychiat. **64**:29 (July) 1950.

5. Porter, E. L., and Taylor, A. N.: Facilitation of the Flexion Reflex in Relation to Pain After Nerve Injuries (Causalgia), J. Neurophysiol. **8**:289, 1945.

6. Koll, W., and Reffert, H.: Eine neue Methode zur Messung analgetischer Wirkungen im Tierversuche mit Morphin und einigen Morphinderivaten am Hund, Arch. exper. Path. u. Pharmakol. **190**:687, 1938.

After completion of preliminary studies on the effects of single doses of morphine and methadone, Dog 66 was addicted[7] to morphine over a period of 41 days by injection of the drug (5 mg. per kilogram of body weight) once daily for 5 days, then twice daily for the next 14 days, and four times daily for 22 days. Morphine was then withheld, and the abstinence syndrome was observed for 40 hours, after which the former dose schedule (morphine sulfate, 5 mg. per kilogram of body weight every 6 hours) was resumed. After 6 days on this schedule, 2 mg. of methadone hydrochloride per kilogram of body weight was substituted for morphine, and injections of this drug were continued every 6 hours for 35 days, when abrupt withdrawal was again carried out. Occasional single injections of methadone were administered during the course of the abstinence syndrome which the animal exhibited during the next 14 days. Twenty-eight days after withdrawal of methadone, the preparation appeared to have recovered fully, and it was then readdicted to morphine for 55 days, by injections of the drug every 6 hours, beginning with 5 mg. per kilogram for 9 days, then 10 mg. per kilogram for 11 days, 15 mg. per kilogram for 8 days, 20 mg. per kilogram for 19 days, and, finally, 25 mg. per kilogram for 8 days, after which the administration of the drug was terminated abruptly. Observations were continued for the duration of the ensuing abstinence syndrome (10 to 14 days) and during the subsequent recovery period. Occasional single injections of morphine and methadone were administered during this time.

After preliminary studies on the effects of single doses of morphine and methadone, Dog 75 was addicted to methadone for a 64-day period by injection of the drug every 6 hours, beginning with doses of 2 mg. per kilogram of body weight for 14 days, then 3 mg. per kilogram for 14 days, 4 mg. per kilogram for 9 days, and 5 mg. per kilogram for 27 days. An attempt was then made to withdraw methadone abruptly, but at about the 18th hour of abstinence the animal was prostrated, and repeated injections of the drug had to be administered to prevent death. After readdicting the animal to 5 mg. of methadone hydrochloride per kilogram of body weight every six hours for four days, withdrawal of the drug was accomplished by rapid reduction of the dose over a period of three days. Observations were continued during the 18-day period of abstinence which ensued and during the subsequent recovery period. Six months after withdrawal of methadone, the animal was addicted to morphine over a period of 76 days by injections of 5 mg. of the drug per kilogram once daily for 40 days, and every 6 hours for the next 36 days, after which morphine was withdrawn abruptly and completely. The dog died on the third day of abstinence.

RESULTS

A. Single-Dose Studies.—1. Temperature and Cardiac and Respiratory Rates: Single injections of morphine or methadone invariably reduced body temperature and cardiac and respiratory rates in both chronic decorticated dogs. The magnitude of such effects appeared to depend on the dose of the drug used and on the initial levels of these variables. When the latter were high, the depressant effects of a given dose of morphine or methadone were more pronounced (Fig. 1). The duration of such effects varied directly as the dose, from four to eight hours.

2. Tooth-Pain-Reaction Thresholds: Tooth resistances between the bipolar electrodes varied from 40,000 to 100,000 ohms, both before and after medication; but, surprisingly, such changes were not correlated with voltage-threshold levels. The latter, however, were modified by a number of factors, of which the most apparent were the preinjection-threshold level and the dose of morphine or methadone.

In general, when preinjection thresholds were high (over about 1.5 volts), they were less reproducible, while the effects of a given dose of either morphine or methadone were more marked, though they varied greatly on different days. When the preinjection thresholds were low (under 1.5 volts), they were far more stable,

7. In this paper, the term "addiction" or "addicted" implies only that morphine or methadone was administered repeatedly on a regular schedule once to four times daily.

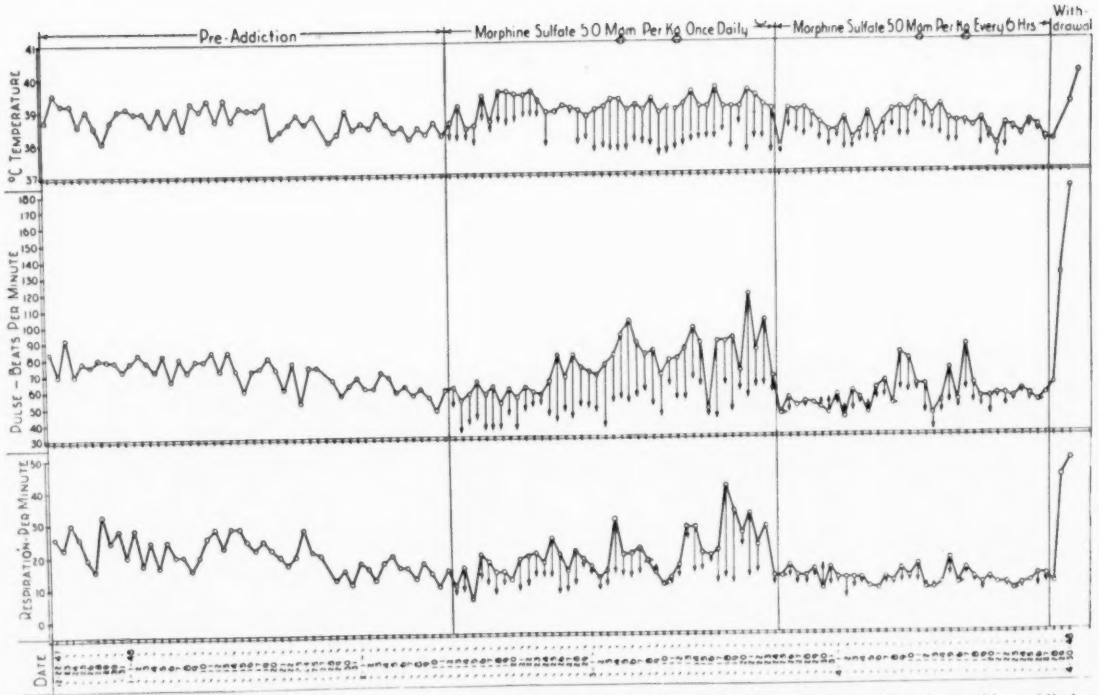


Fig. 1 (Dog 75, chronic decorticate preparation). — Temperature, pulse, and respirations during a cycle of morphine addiction. Note lowering of body temperature, slowing of cardiac rate, and reduction of respiratory rate after each injection of morphine sulfate (5 mg. per kilogram of body weight). There is little evidence of tolerance to the effects of this dose after daily injection of the drug for 40 days. However, when the same dose of morphine was administered every six hours, tolerance to the hypothermic effect of the drug developed rapidly; levels of cardiac and respiratory rates remained low. After abrupt withdrawal of morphine, the body temperature, as well as the cardiac and respiratory rates, rose rapidly to supernormal levels. The dog died on the third day after abrupt withdrawal of morphine.

and the effects of morphine or methadone were more uniform, though smaller in magnitude.[8] The preinjection-threshold level seemed to be closely correlated with the degree of general irritability which the animal exhibited at the time of testing. Also, a gradual rise in preinjection thresholds was observed with the passage of time after the tooth fillings were made, presumably because of local pathologic changes in the dentine or pulp of the tooth. In Dog 66, tooth-pain-reaction thresholds were obtained prior to, as well as after, decortication. The character of the response was not altered, but its threshold appeared to be elevated slightly after ablation of all neocortex and portions of archicortex. It was not possible to measure the amplitude of the threshold response, but if any change occurred, it appeared to be in the direction of enhancement.

Subject to these factors, 5 or 10 mg. of morphine sulfate and 2 or 5 mg. of methadone hydrochloride, per kilogram of body weight, regularly elevated the tooth-pain-reaction thresholds in both decorticated dogs. The effects of 2 mg. of morphine sulfate per kilogram were less predictable. When the initial threshold was high, this dose of morphine elevated it consistently; when the preinjection threshold was as low as 0.9 volt, the small dose of morphine appeared to have no effect in many experiments. The effects of single doses of morphine or methadone on tooth-pain-reaction thresholds in Dog 66 are shown in Figure 2. In Dog 75, preinjection thresholds were about 1.3 volts; average peak thresholds after morphine or methadone were as follows: morphine sulfate, 5 mg. per kilogram, 2.9 volts; morphine sulfate, 10 mg. per kilogram, 4.6 volts; methadone hydrochloride, 2 mg. per kilogram, 2.2 volts; methadone hydrochloride, 5 mg. per kilogram, 5.5 volts. Before injection of either drug, the thresholds for twitching of the skeletal muscle of the lower lip ("lip twitch"), localized piloerection, and, often, head withdrawal were practically identical. After injection of morphine or methadone, the threshold for piloerection was much less elevated than that for lip twitch or head withdrawal. The duration of the effects of morphine or methadone on tooth-pain reaction thresholds varied directly as the dose, but, in general, it was somewhat shorter than the duration of effects on temperature, cardiac and respiratory rates, and spontaneous motor activity.

3. Spontaneous Motor Activity: Immediately after injection of morphine or methadone, in all doses used, a transient increase in "circling" activity was observed, usually associated with vomiting and/or defecation. Such hyperactivity subsided after 15 to 20 minutes, and therefore spontaneous motor activity was greatly reduced for 6 to 12 hours. When thus sedated, the animal usually exhibited extension of the forelegs, with strong positive supporting reactions and semiflexion of the hindlegs. If prodded into activity, the sedated preparations exhibited the "hyenoid" gait which is characteristic of intact dogs after administration of morphine or methadone. The magnitude and duration of effects of these drugs on spontaneous motor activity, posture, and gait varied directly as the dose.

4. Behavioral Responses: In both decorticated preparations, restraint or nociceptive stimulation (e. g., pinching of the toes) evoked furious "sham-rage" responses.[4] Although autonomic components of such response patterns were evident,

8. Such variations in tooth-pain-reaction thresholds and the effects of analgesics thereon have also been observed in intact dogs (Altschul, S., and Wikler, A.: Unpublished data).

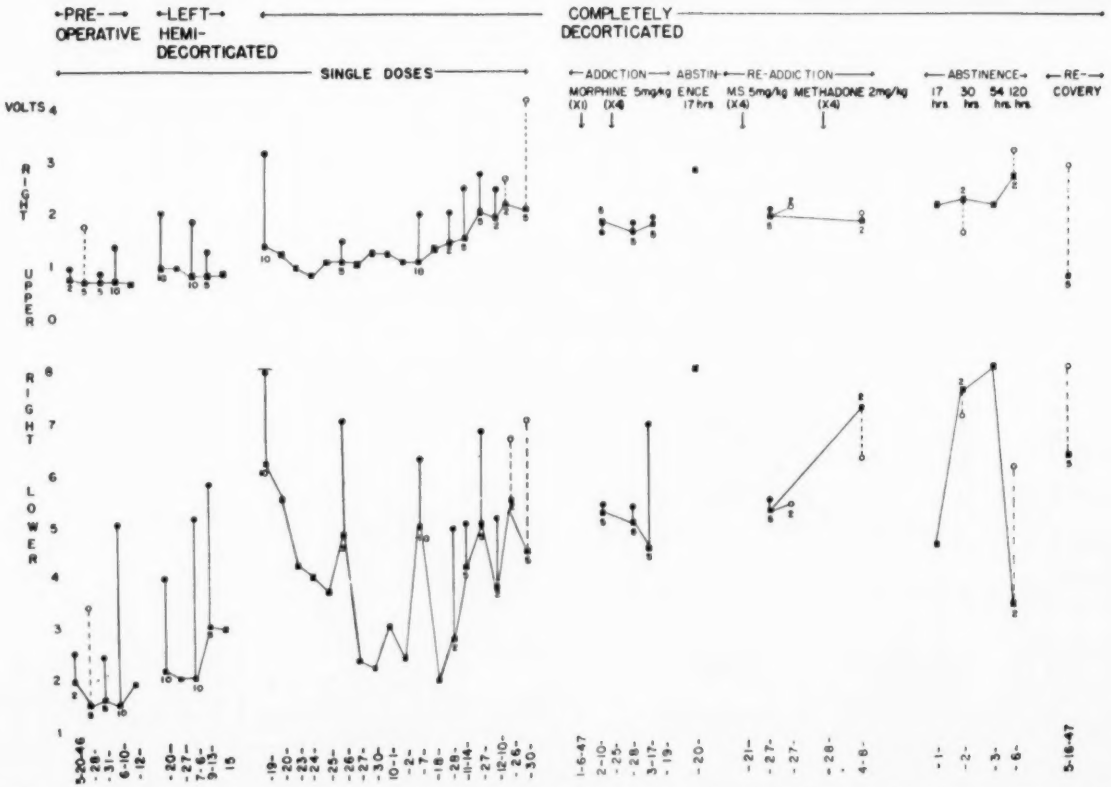


Fig. 2.—Effects of morphine and methadone on tooth-pain-reaction thresholds (fillings made May 17, 1946) in Dog 66, before decortication, after left hemidecortication (operation, June 12, 1946) and after right hemidecortication (operation, Sept. 15, 1946). Numerals indicate dose, in milligrams per kilogram of body weight; squares, preinjection thresholds; solid circles, solid lines, changes in threshold after injection of morphine; outline circles, dash line, changes after injection of methadone. In the right upper canine tooth (low initial thresholds) thresholds were slightly higher after complete decortication, but were fairly reproducible, and the effects of drugs were consistent. Note threshold-raising effects of morphine sulfate (5 and 10 mg. per kilogram) and of methadone hydrochloride (2 and 5 mg. per kilogram), both before and after decortication; tolerance to such effects during addition; spontaneous rise in threshold during the withdrawal period; lowering of the threshold after a single injection of methadone hydrochloride (2 mg. per kilogram), and return to the preaddiction level and loss of tolerance after recovery. In the right lower canine tooth (high initial thresholds) changes are erratic.

it was difficult to estimate the effects of drugs thereon; consequently, only the skeletal motor components will be referred to in this study. These were regularly depressed by all doses of morphine or methadone used after the initial period of hyperexcitability had passed. Of all the skeletal motor components of "sham-rage," vocalization was least affected, while struggling was greatly reduced. The magnitude and the duration of such depressant effects of morphine or methadone varied directly as the dose.

B. Addiction and Withdrawal.—1. Body Temperature, and Cardiac and Respiratory Rates: In both decorticated dogs, tolerance to the hypothermic effects of morphine or methadone developed rapidly when injections of the drugs were administrated every six hours. Tolerance to this effect was less evident when injections were administered once daily (Fig. 1). There was no conclusive evidence of the development of tolerance to the cardiac-rate-slowing and respiration-depressant effects of these drugs, since such variables remained at subnormal levels throughout the periods of addiction. After abrupt withdrawal of morphine or methadone following a period of addiction to the corresponding agent, body temperature and cardiac and respiratory rates rose rapidly to supernormal levels (Fig. 1) and then subsided gradually over a period of five to seven days in all instances, except during the last addiction cycle in Dog 75, which terminated fatally. When a single dose of morphine or methadone was injected during the withdrawal period, the body temperature and cardiac and respiratory rates were reduced promptly for the duration of action of the drug administered.

2. Tooth-Pain-Reaction Thresholds: In both decorticated dogs, clear evidence of the development of marked tolerance to the threshold-raising actions of morphine or methadone was observed during periods of regular injections of either drug once daily, as well as four times daily, when measurements were made on teeth with low control-threshold levels. When the latter were high, variable changes occurred during addiction. Changes in threshold for Dog 66 are shown in Figure 2. In Dog 75 thresholds became stabilized at a level of about 2.5 volts during methadone addiction, and no significant changes were observed after administration of the regular dose of this drug. In both animals abrupt withdrawal of morphine or methadone was followed by a spontaneous rise in tooth-pain-reaction threshold, which could be correlated fairly well with decrease in general irritability (see below). At such times single injections of either drug lowered the elevated thresholds, and this change was correlated with an increase in general irritability (see below). In Dog 66 the pain-reaction threshold of the right upper canine tooth (low control threshold) returned to a level approximating that of the preaddiction period, while that of the right lower canine tooth (high control threshold) remained erratic (Fig. 2). In Dog 75 tooth-pain-reaction thresholds returned to a level of about 1.8 volts after full recovery from methadone addiction.

3. Spontaneous Motor Activity: During addiction, the depressant effects of morphine or methadone on spontaneous circling became progressively less marked. In Dog 66 tolerance developed rapidly to the depressant effects of 5 mg. of morphine sulfate per kilogram once daily or every six hours, and cross tolerance to methadone hydrochloride, 2 mg. per kilogram, was almost complete. In Dog 75

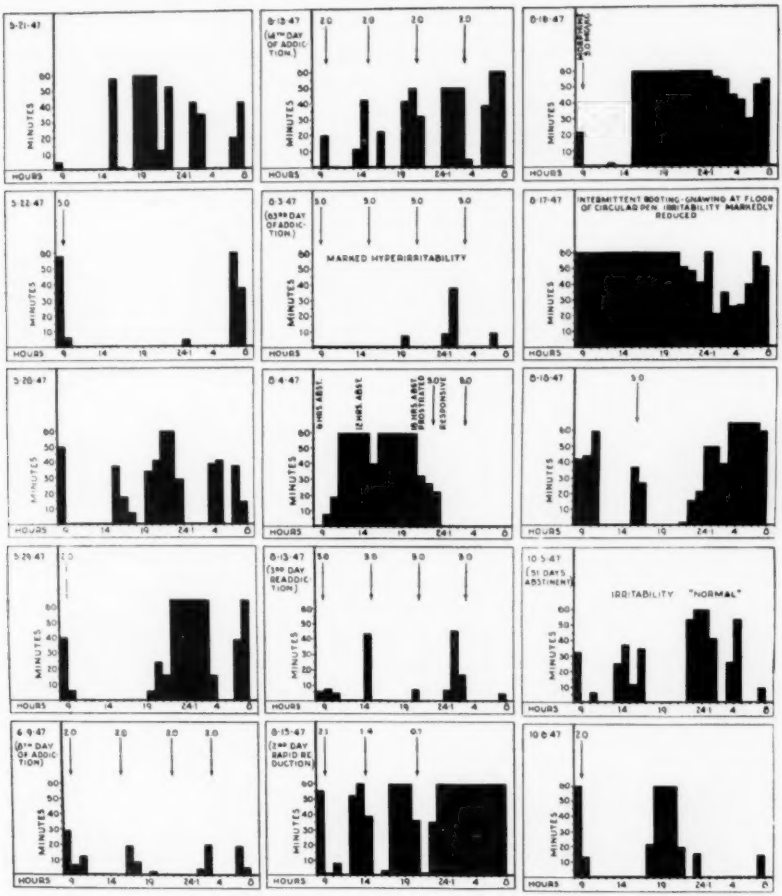


Fig. 3 (Dog 75, chronic decorticate preparation).—Sample records of spontaneous circling activity during addiction to methadone. Numbers indicate dose, in milligrams per kilogram of body weight; ordinates, minutes of circling; abscissa, each of the 24 hours of the day.

Single dose studies were as follows: Controls (May 21 and May 28, 1947); effects of methadone hydrochloride, 5 mg. per kilogram (May 27), 2 mg. per kilogram (May 9, 1947). Note reduction of circling.

Addiction studies: Note development of tolerance to effects of 2 mg. per kilogram every six hours (June 9 and June 15, 1947); tolerance to 5 mg. per kilogram every six hours developed at a slower rate and was incomplete (Aug. 3 and Aug. 13, 1947).

Withdrawal studies: Note marked increase in circling, changes in irritability, and peculiar behavior (Aug. 4, Aug. 15, and Aug. 18, 1947). Marked changes also occurred in body temperature and pulse and respiration rates (see text). At the height of the abstinence syndrome, single injections of methadone hydrochloride, 5 mg. per kilogram, reduced hyperactivity and other withdrawal signs and restored irritability (Aug. 4 and Aug. 18, 1947).

Recovery studies: Note return to preaddiction pattern of spontaneous circling activity (Oct. 5, 1947) and partial loss of tolerance to effects of methadone hydrochloride, 2 mg. per kilogram (Oct. 6, 1947).

tolerance to 2 mg. of methadone hydrochloride per kilogram every six hours developed rather rapidly, but complete tolerance to 5.0 mg. of the drug every six hours was not complete, even at the end of the addiction study (Fig. 3). In contrast, tolerance to 5 mg. of morphine sulfate every six hours developed rapidly (Fig. 4). As tolerance developed, circling activity increased steadily before each injection and

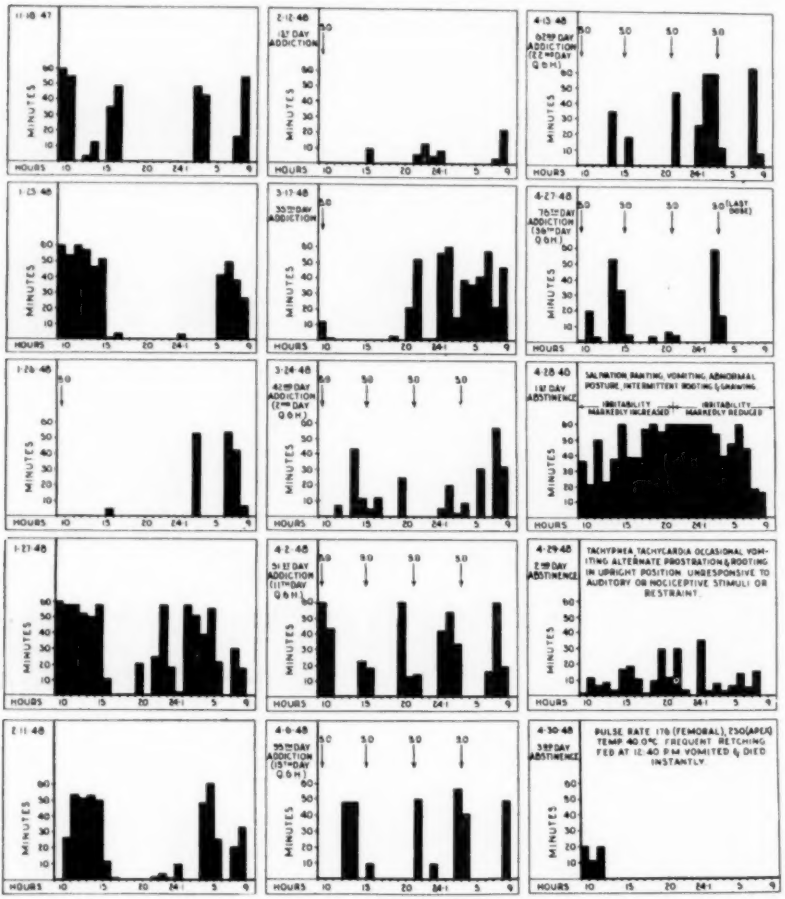

MINUTES
HOURS
SALIVATION, PANTING, VOMITING, ABNORMAL POSTURE, INTERMITTENT ROOTING & GNAWING
IRRITABILITY MARKEDLY INCREASED
IRRITABILITY MARKEDLY REDUCED
TACHYPNEA, TACHYCARDIA, OCCASIONAL VOMITING, ALTERNATE PROSTRATION & ROOTING IN UPRIGHT POSITION, UNRESPONSIVE TO AUDITORY OR NOCICEPTIVE STIMULI OR RESTRAINT.
PULSE RATE 170 (FEMORAL), 230 (APEX), TEMP. 40.0°C, FREQUENT RETCHING, FED AT 12:40 P.M. VOMITED & DIED INSTANTLY.

Fig. 4 (Dog 75, chronic decorticate preparation).—Sample records of spontaneous circling activity during addiction to morphine. Symbols, etc., are as in Figure 3.

Single dose studies: Controls, (Nov. 18, 1947; Jan. 25, 1948; Feb. 11, 1948); effects of morphine sulfate, 5 mg. per kilogram (Jan. 26 and Feb. 12, 1948). Note reduction in circling.

Addiction studies: Note development of marked tolerance to 5 mg. per kilogram every six hours and increase in preinjection circling by 51st day of addiction (April 2, 1948).

Withdrawal studies: Note abstinence changes (April 28 and 29, 1948), similar to those after abrupt withdrawal of methadone (Fig. 3). The dog died on the third day after abrupt withdrawal of morphine (April 30, 1948).

subsided after the drug was administered. Abrupt withdrawal of either drug in both decorticated dogs was followed by consistent changes in spontaneous motor activity, which proceeded in four stages: (*a*) an initial increase in circling, which was a continuation of the usual preinjection restlessness; (*b*) a period of quiescence, lasting 1 to 2 hours; (*c*) a prolonged period of incessant circling, lasting as long as 48 hours (Figs. 3 and 4), after which the animal was either exhausted or engaged in activities which prevented circling (see below), and (*d*) gradual subsidence of circling to a level approximating the control values, over a period of 7 to 10 days. On abrupt withdrawal of methadone, Dog 66 exhibited all four stages. However, after the subsequent period of addiction to morphine, abrupt withdrawal of the drug was followed by little circling, since the dog maintained peculiar postures, with hindlegs flexed forward under the forelegs, so that, although restless, the animal "turned somersaults" repeatedly. Peculiar postures were also exhibited by Dog 75, but these did not prevent circling.

4. Behavioral Changes: As tolerance developed, the depressant effects of morphine or methadone on "sham rage" became less marked in both decorticated dogs, and, concomitantly, they became increasingly irritable 1 to 1½ hours before each regular injection. When tolerance was well developed, merely touching the animal evoked furious "sham-rage" responses before each dose of the drug. Abrupt withdrawal of either drug in both decorticated dogs was followed by a strikingly stereotyped series of changes, which may be divided into four states, corresponding roughly with those described above: (*a*) initial increase in irritability; (*b*) further increase in irritability, accompanied by yawning, rhinorrhea, salivation, vomiting, and maintenance of peculiar postures; (*c*) intermittent sniffing, rooting, and gnawing at the floor of the pen, usually in the corner formed by the floor and wall, which was associated with a marked reduction in irritability and almost complete absence of "sham-rage" responses, and (*d*) gradual subsidence of such changes and return to preaddiction patterns of behavior. Stage *c* was characterized by a rather striking picture, since such persistent gnawing and rooting was never observed in these animals at any other time. In Dog 75 pressure necrosis of a portion of the upper lip actually developed during this period. The animal, moreover, appeared to be in circulatory collapse and in danger of imminent death at this stage, after abrupt withdrawal of methadone. Within 30 minutes after injection of a single dose (5 mg. per kilogram) of this drug, the animal's femoral pulse could be palpated again, and it sat up and exhibited "sham rage" on handling. Similar, though less dramatic, effects were observed repeatedly in both dogs during this stage of the abstinence syndrome after injections of single doses of morphine or methadone. It is noteworthy that such "restituting" effects of these drugs are precisely the opposite of the actions of these agents prior to, and after recovery from, addiction.

COMMENT

These data indicate that tolerance to, and "physical dependence" on, morphine or methadone can be developed in dogs in the complete absence of neocortex and portions of the archicortex. In fact, the changes in physiologic variables which are observed in decorticated dogs are of the same general nature as those which are

noted in intact dogs,[9] except that in the absence of neocortex, the morphine- or methadone-abstinence syndrome is more stereotyped, and also severer. The significance of these findings has been discussed elsewhere, with reference to problems concerned with the sites and mechanisms of the action of morphine in the central nervous system.[10]

Of particular relevance to clinical problems in drug addiction, however, is the fact that "physical dependence" on narcotic drugs can be demonstrated in animals whose capacity to "learn" has been reduced drastically.[4] The fact that "physical dependence" can be demonstrated in the rat,[11] dog,[9a] monkey,[12] and chimpanzee[13] does not exclude the possibility that this phenomenon is entirely "psychogenic," if by this term is meant that the genesis of the opiate-abstinence syndrome is related not to the direct pharmacologic effects of this class of drugs, but to the "meanings" which such effects have for the animal. However, in decorticated dogs the genesis of the opiate-abstinence syndrome must be related to changes in the organism which are due to the immediate and delayed direct pharmacologic actions of the drugs in question, and not to factors of symbolic significance. This inference does not preclude the possibility that such "unconditioned" changes may become "conditioned" in the intact animal or in man, and that clinically "physical dependence" may be partly "psychogenic" and partly "organic."[14] Therefore it would be preferable to subsitute the terms "nonpurposive" and "purposive" abstinence changes for terms such as "physical" and "psychic" dependence.

The results of these studies also provide further evidence that methadone, one of the newer potent synthetic analgesics, is capable of producing "physical dependence," although in man the methadone-abstinence syndrome is milder than that of morphine.[15] Corroborative evidence of the "physical dependence"-producing liability of methadone has also been obtained from studies on chronic spinal dogs.[16]

The observations on the lip-twitch responses to electrical stimulation of a tooth are of interest also in relation to problems in the methodology of analgesic testing procedures. It is evident that this response, which is the basis of some analgesic

9. (*a*) Pierce, I. H., and Plant, O. H.: Studies on Chronic Morphine Poisoning in Dogs: III. Blood Sugar During Tolerance and Withdrawal, J. Pharmacol. & Exper. Therap. **33**:371-385, 1928. (*b*) Wikler, A., and Frank, K.: Tolerance and Physical Dependence in Intact and Chronic Spinal Dogs During Addiction to 10820 (4-4-Diphenyl-6-Dimethylamino-Heptanone-3), Federation Proc. **6**:384, 1947.

10. Wikler, A.: Sites and Mechanisms of Action of Morphine and Related Drugs in the Central Nervous System, Pharmacol. Rev. **2**:435, 1950.

11. Himmelsbach, C. K.; Gerlach, G. H., and Stanton, E. J.: A Method for Testing Addiction, Tolerance and Abstinence in the Rat, J. Pharmacol. & Exper. Therap. **53**:179, 1935.

12. Seevers, M. H.: Opiate Addiction in the Monkey: I. Methods of Study, J. Pharmacol. & Exper. Therap. **56**:147, 1936.

13. Spragg, S. D. S.: Morphine Addiction in Chimpanzee, Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1940, Vol. 15, p. 1.

14. Wikler, A.: Recent Progress in Research on the Neurophysiologic Basis of the Morphine Abstinence Syndrome, Am. J. Psychiat. **105**:329, 1948.

15. Isbell, H.; Wikler, A.; Eisenman, A. J.; Daingerfield, M., and Frank, K.: Liability of Addiction to 6-Dimethylamino-4-4-Diphenyl-3-Heptanone (Methadon, "Amidone" or "10820") in Man, Arch. Int. Med. **82**:362-392 (Oct.) 1948.

16. Wikler, A., and Frank, K.: Hindlimb Reflexes of Chronic Spinal Dogs During Cycles of Addiction to Morphine and Methadone, J. Pharmacol. & Exper. Therap. **94**:382, 1948.

testing methods,[17] is integrated subcortically, and that the depressant effects of analgesic agents thereon are due, at least in part, to subcortical actions. In general, this seems to be true of all the current analgesic testing methods on animals, for it has been shown that other representative responses to nociceptive stimulation, such as the tail flick in the rat [18] and the skin twitch in the dog,[19] are spinal reflexes. However, the depressant action of opiates on the tail flick and the skin twitch appear to be due partly to direct depressant actions on the spinal cord, and partly to augmentation of supraspinal inhibitory mechanisms. It was not possible to determine whether augmentation of cortical inhibition plays a role in the depression of the lip-twitch response to electrical stimulation of a tooth-pulp nerve in intact animals, since the amplitudes of the responses were not measured, and comparisons of depressant drug effects on "thresholds" yield unreliable results for such purposes.[19]

SUMMARY AND CONCLUSIONS

Measurements of body temperature, cardiac and respiratory rates, tooth-pain-reaction thresholds, spontaneous motor activity, and behavioral responses to restraint and to nociceptive stimulation were studied during complete addiction cycles in two chronic decorticated dogs. Supportive data were also obtained in studies during partial addiction cycles in 11 other decorticated dogs.

Single doses of morphine or methadone regularly lowered body temperature and cardiac and respiratory rates, elevated tooth-pain-reaction thresholds, and reduced spontaneous circling and "sham-rage" responses.

During periods of regular, continuous injection of morphine or methadone, tolerance developed to the effects of these drugs on body temperature, tooth-pain-reaction thresholds, spontaneous circling, and "sham-rage" responses. Methadone (2 mg. per kilogram) substituted readily for morphine (5 mg. per kilogram) when tolerance to the latter had been established. However, tolerance to 5 mg. of methadone per kilogram of body weight four times daily was not developed completely during the periods of addiction employed in these studies.

After abrupt withdrawal of either morphine or methadone, stereotyped abstinence syndromes developed, which were characterized by (*a*) an initial period of increased circling, associated with increased general irritability; (*b*) a period of quiescence, associated with further increase in irritability and exhibition of yawning, rhinorrhea, and salivation; (*c*) a period of incessant circling, associated with rise in body temperature, cardiac and respiratory rates, vomiting, maintenance of peculiar postures, gnawing and rooting, marked diminution in irritability, and elevation of tooth-pain-reaction thresholds; (*d*) gradual subsidence of these changes over a two-week period, with return to preaddiction levels of measurements and patterns of behavior. During Stage *c*, single doses of morphine or methadone reduced elevated physiologic variables, and, concomitantly, they enhanced general irritability.

17. Koll and Reffert.[6] Goetzl, F. R.; Burrill, D. Y., and Ivy, A. C.: Critical Analysis of Algesimetric Methods, Quart. Bull. Northwestern Univ. M. School, **17**:280, 1944.

18. Irwin, S.; Houde, R. W.; Bennett, D. R.; Hendershot, L. C., and Seevers, M. H.: Effects of Morphine, Methadone and Meperidine on Some Reflex Responses of Spinal Animals to Nociceptive Stimulation, J. Pharmacol. & Exper. Therap. **101**:132, 1951.

19. Houde, R. W., and Wikler, A.: Delineation of Skin-Twitch Response in Dogs and Effects Thereon of Morphine, Thiopental and Mephenesin, J. Pharmacol. & Exper. Therap. **103**:236, 1951.

True "physical dependence" can be studied only in animal preparations, such as decorticated or spinal dogs, which are incapable of responding to meaningful stimuli. The present findings indicate that the genesis of "physical dependence" during morphine or methadone addiction is related, at least in part, to nonmeaningful, pharmacologic effects of the drugs in question, and not exclusively to factors of symbolic significance. In intact animals and in man, it would be preferable to substitute "nonpurposive abstinence changes" and "purposive abstinence changes" for the terms "physical dependence" and "psychic dependence," which are now in current use.

The demonstration that repeated injections of methadone can produce true "physical dependence" in chronic decorticated dogs, as well as in chronic spinal dogs, supports clinical evidence that the regular use of this drug is associated with addiction liability in man.

In the dog, the lip-twitch response to electrical stimulation of a tooth-pulp nerve is integrated subcortically, and the depressant effects of analgesic agents thereon in the intact animal are due, in part at least, to subcortical actions of these drugs.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Hugh T. Carmichael, M.D., *President, in the Chair*
Regular Meeting, Jan. 8, 1952

Involvement of the Peripheral Nerves in Diffuse Collagen Disease: A Clinical-Pathologic Report. DR. RICHARD B. RICHTER.

It is not generally appreciated that severe polyneuropathy not only may appear in the more chronic forms of diffuse collagen disease, such as scleroderma, but may even dominate the clinical picture in such a way as to obscure the diagnosis.

This report is based upon an account of two patients whose symptoms and signs were primarily those of severe progressive polyneuropathy, chronic in one and subacute in the other. In neither patient were there obvious or characteristic manifestations generally considered diagnostic of any of the usual forms of collagen disease, acute or chronic; and no other cause for the neuropathy could be discovered.

In the patient having the most advanced and long-standing neuropathy, autopsy revealed that the main abnormalities were in the connective tissues of the body, consisting in a great increase in the bulk and proportions of the collagen tissues. The fibrosing process was most striking in the retroperitoneal, mediastinal and pelvic areolar tissues, but there was a well-marked scleroderma as well. Throughout the peripheral nerves of the extremities there was almost complete degeneration of the nerve fibers, associated with extreme overgrowth of the collagen of the epineurium, perineurium, and endoneurium, so that the nerve bundles were incarcerated in the sclerotic tissue.

Biopsy of tissue from the second patient revealed connective-tissue degeneration in the shin and myositis.

Both patients had previously been treated for syphilis on the basis of a positive Wassermann reaction of the blood alone. Both patients had a negative Wassermann reaction of the spinal fluid, and in the first patient no lesions identifiable as syphilitic were observed at autopsy. Both patients also exhibited hyperpigmentation of the skin, sufficiently intense to suggest a diagnosis of Addison's disease. There was, however, no pigmentation of the buccal mucosa or arterial hypotension, and the serum electrolytes were normal. It is emphasized that a positive serologic reaction of the blood and a negative Wassermann reaction of the spinal fluid without convincing clinical evidence of syphilis, and pigmentation of the skin in the absence of other signs of Addison's disease, may be important clues to a correct diagnosis of diffuse collagen disease.

Clinical Pathologic Study of Hallervorden-Spatz Syndrome. DR. RUSSELL N. DE JONG.

The Hallervorden-Spatz syndrome is a rare condition, occurring mainly in children and usually familial. The symptoms described include rigidity, spasticity, choreoathetoid movements, and mental deficiency. The outstanding pathologic alterations have been depositions of pigment in the globus pallidus and the reticular zone of the substantia nigra, along with degeneration and demyelination of the globus pallidus. In addition, in many cases there have been degenerative changes in the cerebral cortex and the cerebellum.

The case presented was that of a boy who had developed slowly and who had always had some difficulty with coordination and speech. At about the age of 7 or 8 years he exhibited severe ataxia and increasing difficulty with speech and failed to progress in school. Examination revealed profound ataxia and dysarthria; flaccid extremities, hyperactive deep reflexes, and some facial grimacing.

As the disease progressed, the patient showed increasing intellectual deterioration and the development of some increased tone in the distal portions of the extremities. He also had minor seizures.

Autopsy, carried out after his death, at the age of 13, showed pronounced thickening of the skull and atrophy of the cerebrum and cerebellum. On coronal section, the globus pallidus appeared greenish-brown, the gray matter of the hemispheres was narrow, and the white matter was atrophic; there was advanced atrophy of the gray matter of both cerebellar hemispheres. Histologic examination of the brain showed numerous black-pigment deposits throughout the entire globus pallidus and the reticular zone of the substantia nigra. There was a dense glial scar throughout the pallidum, with reduction of the neurons and rarefaction of the myelin. The pigmented areas stained heavily for both iron and lipid. The cerebral cortex showed atrophy and severe architectural changes, with glial proliferation. In the white matter there were atrophy, with rarefaction of myelin, and some areas of necrosis. The cerebellum exhibited severe degeneration with reduction in the number of the Purkinje cells and severe changes in both the molecular and the granular layer.

The condition described by Hallervorden and Spatz should be considered a syndrome, not a disease. The essential pathologic alterations are the pigment deposits in the globus pallidus and the reticular zone of the substantia nigra. While the outstanding clinical manifestations in the present case were flaccidity and ataxia, instead of rigidity and athetosis, the pathologic alterations conform to those which have been described by Hallervorden, Spatz, and others.

Symptomatology of Variously Located Seizure Discharges. Dr. Frederic A. Gibbs.

Electroencephalography has paved the way for a new type of neurology—a dynamic neurology based on the study of dysfunction and hyperfunction. The symptomatology of discharging lesions is at least as interesting as the symptomatology of structural defects.

The commonness with which certain symptoms appear as a result of focal epileptic discharge (electroencephalographically demonstrated) in certain areas of the brain has been determined from the analysis of a large group of cases. Certain supposedly valid localizing signs must be reevaluated in the light of newer evidence, and some supposedly nonlocalizing signs can now be accepted as having localizing value. Seizures of the Jacksonian type are not a reliable sign of an epileptic focus in the central cortical area, for they are more commonly associated with a focus in the midtemporal lobe than with one in the central area. Trance-like attacks and confusional episodes are a reliable sign of seizure activity in the anterior temporal region. Strabismus in patients with epileptic seizures suggest an occipital focus of seizure activity.

Discharging lesions tend to have different forms and different locations in different age groups. Occipital foci are particularly common in infants, and midtemporal-lobe foci in children; both tend to disappear with increasing age. Foci in the anterior temporal lobe are common in adults, and they account for by far the commonest type of focal epilepsy.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Harold G. Wolff, M.D., President, New York Neurological Society, Presiding

Joint Meeting, Dec. 11, 1951

Observations on "Rehabilitation" of the Neurologically Handicapped. Dr. Edward B. Schlesinger.

Since World War II, with its backwash of the severely handicapped, there has been a vigorous recrudescence of interest in the lot of the chronically disabled.

This report consisted in the description of stress breakdown in a series of patients undergoing intensive rehabilitation therapy. The series included five patients with median and ulnar paresis, one with axillary thrombosis, three with the scalenus anticus syndrome, and one with coronary occlusion incident to the patient's mobilization in the course of the establishment of ambulation and self-care. Incomplete, but important, statistics on the follow-up of successfully trained patients were offered to clarify the long-term outlook in cases of chronic disablement.

The impression gained is that spiritual goals, set by enthusiastic workers, do not take sufficiently into account the dynamic architecture of the human mechanism and its stress limitations. Caution in exceeding the maximum load is as important in the human body as in the machine.

DISCUSSION

DR. ROBERT C. DARLING: Dr. Schlesinger's observations and their presentation are thoroughly honest and sincere, and, if you will, a bit courageous, for he is opposing a certain trend.

I should like to pose one question: What is harmful stress? Sometimes physicians tend to think that any stress is harmful; I should like to decry that point of view. Unfortunately, there are available few measurable criteria for judging the harmfulness of stress.

A well-balanced rehabilitation program, in my opinion, should include three chief features. All agree that development of physical competence in self-care and ambulation within the framework which has been outlined, including a careful judgment of what is harmful in the line of stress, is the first consideration. The second, which is one of the most difficult, is the development of the patient's acceptance of his limited physical capacity. The third, which Dr. Schlesinger touched on briefly, is the evaluation of the patient's assets, rather than his liabilities, and the promotion of their full utilization for life satisfaction and for vocation.

DR. BENJAMIN ROSENBLUTH: Many years ago, on Welfare Island there were the Neurological and Central Hospitals. In these hospitals there were always 200 to 300 neurological cases of all kinds, and we of the staff began to think of rehabilitation, especially of the patients with long-standing locomotor ataxia and multiple sclerosis. Our greatest trouble was that no matter how much we would train these patients, we had to keep up the training continually. We did not have social workers in those days, and the family would stimulate the patient in the way for which Dr. Schlesinger now indicts the therapist. We began to see patients die; those who went home and were subjected to family stimulation, or those in the hospital who were taken over by enthusiastic newly trained therapists, went by the board. I feel the same way about the present patients, so many of whom are being "rehabilitated"; I think it is absurd. It is cruelty, rather than anything else, to train these patients—these hemiplegics—for impossible goals.

DR. LOUIS HAUSMAN: How long were the patients exposed to the stress which produced the peripheral-nerve changes?

DR. EDWARD B. SCHLESINGER: For various periods; it would be difficult to say—some several months; some a year or more.

DR. THOMAS CARR: I wonder how large this series was. It is possible that the patients Dr. Schlesinger refers to are the relatively small tragic minority, rather than the extensive majority.

DR. EDWARD B. SCHLESINGER: It is unquestionably true that these patients are in the minority, but I bring them to the attention of a group of neurologists for the purpose of emphasizing results of this kind. I am not indicting physical medicine or rehabilitation; I merely should like to see more discretion in the patients treated.

DR. ALEXANDER ADLER: As long as we do not know how far we can succeed with rehabilitation, and we often do not know how far a patient can recover, it seems more advisable to have an optimistic, rather than a pessimistic, view and to try to get as far as possible, rather than be overcautious. In so many cases, after something has been achieved, the patient may stop his efforts. One cannot apply a general rule to all patients, but we should adapt our attitude respecting rehabilitation to the individual patient.

DR. HAROLD G. WOLFF: There is a fair price for every therapeutic procedure, and sometimes the price is too high. Is that not your thesis, Dr. Schlesinger?

DR. EDWARD B. SCHLESINGER: Precisely.

DR. THEODORE J. C. VON STORCH, Albany, N. Y.: One group of physical therapists will not attempt to treat multiple sclerosis or progressive disorders. Another group is exceedingly optimistic. I should like to hear Dr. Schlesinger's view. He told me he followed a group of patients who were taken out of the wheel chair and made ambulatory to learn what their status was at home. I wonder whether he would care to tell us what he found.

DR. EDWARD B. SCHLESINGER: I do not want to give the false impression that I think there is something entirely wrong in the use of rehabilitation.

With regard to what Dr. von Storch said, a survey now in process shows a very disappointing follow-up of a group of patients trained literally with blood, sweat, and tears. They no longer

use their braces at all and spend their time in the wheel chair. This is particularly true of patients who have become vocationally successful.

In closing, I should say that rehabilitation is a medical problem which needs critical neurological help, and to date it has not received much. My plea is merely to evoke neurological interest in the problems of rehabilitation before we are again replaced by less eligible observers.

Studies on Index of Platelet Adhesiveness in Multiple Sclerosis and Other Neurological Disorders. Dr. Morton Nathanson and Mr. J. Philip Savitsky.

The index of platelet adhesiveness was determined for 132 patients with the method devised by Moolten and Vroman. Sixty patients had multiple sclerosis; 33 had other chronic neurological disorders, and 39 had various acute neurological disorders. The group with multiple sclerosis was divided into three categories on the basis of clinical activity: stationary activity, fluctuating activity, and acute exacerbation.

The index of platelet adhesiveness was found to be abnormally high in the cases of fluctuating activity (82%) and acute exacerbation (100%) in multiple sclerosis, whereas in only 20% of the stationary cases was the index of platelet adhesiveness elevated. Of the other chronic neurological disorders, the index was abnormally high in only 12%. Of the acute neurological disorders, abnormally high indices appeared in cases of recent head trauma, brain tumors, and the Guillain-Barré syndrome. However, cerebrovascular accidents and inflammatory diseases of the central nervous system gave uniformly normal values.

A change in one of the properties of platelets, namely, the adhesiveness, seems to take place prior to and during clinical activity of multiple sclerosis. Although this is not specific for multiple sclerosis, its occurrence is rare in other chronic neurological disorders.

DISCUSSION

Dr. Richard Brickner: Any definitive procedure that will help in estimating activity in multiple sclerosis is of high value and has been awaited a long time. It would have great importance in estimating therapy. I know of only one previous sound approach in this direction, the immunological work of Sachs and Steiner and of Witebsky.

One of the several reasons for the difficulty in the evaluation of therapeutic measures is that even specific therapy could be effective only while the disease is active; yet there has been no dependable way of recognizing activity and inactivity. The disease may become inactive, I presume, in as short a time as a few minutes, and attacks may come and go as rapidly as that.

Will the authors tell us what dose of cortisone the one patient was receiving when he had his relapse?

Dr. Donald J. Simons: Will Mr. Savitsky repeat the reference to the work of Moolten and Vroman and tell us whether this test is an easy one to perform? How readily is it subject to error?

Dr. Morton Nathanson: I should like to emphasize one point in this work with platelets; we have not tried to show that the pathogenesis is thrombosis; we can only say that a change in one of the properties of the thrombocytes seems to take place prior to or during clinical activity. The test for adhesiveness certainly is not specific for multiple sclerosis, but the high indices of adhesiveness in cases of Guillain-Barré syndrome and of brain tumors, in contradistinction to the indices in cases of cerebrovascular accident and inflammatory diseases of the central nervous system, are of interest.

We have made determinations in several cases of acute allergic conditions; they, too, showed high indices of adhesiveness. Whether or not that is significant we cannot say.

Mr. J. Philip Savitsky: The test for platelet adhesiveness used in this study was devised by Moolten and Vroman (Moolten, S. E., and Vroman, L.: Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders: I. Measurement of Platelet Adhesiveness by the Glass Wool Filter, *Am. J. Clin. Path.* **19**:701-709, 1949). The test is not simple, but a competent worker can master it.

The demonstration of a correlation between rapidity of clot-retraction time and the level of platelet adhesiveness may be of interest. The determination of clot-retraction time under

well-controlled conditions is extremely simple, and when it is more fully worked out it may be of more value than the index of platelet adhesiveness.

In reply to Dr. Brickner, the dose of cortisone was 100 mg. a day.

Results of Electroshock Therapy in Patients over 60 Years of Age. Dr. Curtis T. Prout, and Dr. Donald M. Hamilton, White Plains, N. Y.

Reports were presented of two patients over 60 years of age who had organic complications and were treated with electroshock at the New York Hospital-Westchester Division for mental illness. The cases were presented to illustrate some of the dramatic problems revealed in a study of a group of 104 men and women who had been admitted to that hospital between 1942 and 1948 and who had received varying amounts of treatment. Statistics were reported concerning the types and frequency of organic complications encountered, cardiovascular lesions being present in over two-thirds of the patients prior to this type of therapy.

Important considerations prior to the application of electroshock therapy to patients in this older age group were discussed, and it was reported that four-fifths of the patients in the group studied were able to return home from the hospital as recovered or as much improved.

DISCUSSION

Dr. Harold G. Wolff: I assume there were no deaths in this series.

Dr. Curtis T. Prout, White Plains, N. Y.: That is true.

Dr. H. Houston Merritt: You stressed the examination of the cardiovascular system and stated that most of the patients were given shock therapy, although there were evidences of heart disease. Did you exclude any patients because of the cardiovascular disease?

Dr. Curtis T. Prout: We should exclude patients only temporarily, for further investigation—of course, if the patient is moribund, shock therapy is not used; but if a patient has had evidence of coronary disease in one form or another, our procedure is to wait and watch, with serial electrocardiograms, until there is evidence of healing as indicated electrocardiographically.

Influence of Skin Temperature upon the Pain Threshold as Evoked by Thermal Radiation. Dr. James D. Hardy, Philadelphia; Miss Helen Goodell, and Dr. Harold G. Wolff, New York.

This study was published in *Science* **114**:149-150 (Aug. 10) 1951.

From the observations the close relation of tissue damage to noxious stimulation can be inferred, thus significantly supporting the concept that the adequate stimulus for pain is tissue injury.

DISCUSSION

Dr. Raymond W. Houde: The authors are to be congratulated on their well-conceived experiments and on bringing us a bit closer to the understanding of the physiology of pain. They have added to the growing bulk of evidence indicating that the receptive apparatus in the skin for pain is different from that for heat and cold.

Those of us who are interested in the study of pain must come face to face with the necessity of dealing with phenomena occurring in two distinct frames of reference: one, the psychological, or subjective (in which sensation and pain occur), and the second, the physical, or objective (which is measured in terms of stimulation, or activation, of the neural apparatus).

The evidence presented here is a step forward in indicating the exact nature of the stimulus with regard to pricking pain due to heat applied to the skin, and its correlation with tissue injury is indeed interesting.

I am not sure, however, that the authors mean to imply that tissue injury is necessarily the adequate stimulus for activation of the naked fiber endings which we call the "pain receptors." The lack of correlation between the mere activation of the neural apparatus subserving pain and the sensation evoked raises the possibility that other pains, or at any rate other types of pain, may not necessarily be caused by tissue damage. I should like to hear the authors' views on this subject.

Dr. Morton Nathanson: I should like to ask whether the patients in this study mentioned their being aware of the new stimulus, for example, the cold room. Do the authors believe that

the new stimulus influenced the threshold, since the conditions of testing were changed, in that there were two stimuli. I should like to know whether the subjects responded verbally or otherwise to the cold.

DR. HAROLD G. WOLFF: The subjects all felt the cold in the cold room; they knew they were cold; they were aware also that the skin felt cold.

DR. BENJAMIN ROSENBLUTH: Are the spots of pain developed by heat the same spots of pain as those developed by pinprick?

DR. HAROLD G. WOLFF: That point was not investigated; the area that was stimulated was so large (approximately 1 cm.) that many spots were stimulated at the same time and it was not possible for us to differentiate whether burning and pricking pain were from the same spot.

DR. THEODORE J. C. VON STORCH, Albany, N. Y.: Do the authors wish to imply that tissue damage is necessary for the production of this type of pain?

DR. HAROLD G. WOLFF: I should say that pain is the result of the tissue damage, although the tissue damage may be very slight and completely reversible.

DR. BENJAMIN ROSENBLUTH: How is the tissue damage evaluated?

DR. HAROLD G. WOLFF: It can be appraised only when the stimulus is sufficiently long that there is erythema. The fact of the damage was correlated with observations by others that at the same skin temperature at which a certain amount of protein change occurred, threshold pain from thermal stimulation was perceived.

DR. BENJAMIN ROSENBLUTH: How was that ascertained?

MISS HELEN GOODELL: Experiments were carried out on excised pieces of skin to determine the coagulation time of tissue substances.

DR. IGNAZ W. OLJENICK: Do you think that room-temperature stimuli are important; does that also agree with your theory that tissue damage is necessary for producing cold pain?

DR. HAROLD G. WOLFF: Pain was produced at all temperatures; we assume that tissue damage was necessary for all.

MISS HELEN GOODELL: Dr. Oljenick, I am afraid we are not yet able to answer your question. Cold pain occurs in two sets of circumstances: When a hand is immersed in ice water, a very intense pain is first associated with vasoconstriction, as measured by a plethysmograph. If the hand is left in the ice water, the pain disappears; and if it is kept there the pain returns. At that time measurements show the skin temperature to be elevated, together with vasodilatation. Thus, cold pain is not due to vasoconstriction or to vasodilatation, itself, but just what the adequate stimulus for cold pain is has not yet been discovered.

DR. HAROLD G. WOLFF: Would you say it was the amount of tissue damage or the rate of tissue damage which determines the intensity of the pain?

MISS HELEN GOODELL: It may be a combination of the two, but for the most part it is the rate at which damage to tissue occurs.

DR. HAROLD G. WOLFF: I agree that the rate of damage is related to the intensity of pain, for one can have a great deal of tissue damage without any pain.

PHILADELPHIA NEUROLOGICAL SOCIETY

Michael Scott, M.D., Presiding
Regular Meeting, Dec. 7, 1951

Effects of Trihexyphenidyl (Artane®) on the Electroencephalogram in Paralysis Agitans. DR. AARON W. MALLIN, DR. ISADORE ROSE (by invitation), and DR. JOSEPH F. HUGHES.

This report represented further study at the Philadelphia General Hospital of the electroencephalographic changes in patients with known pathologic involvement of the basal ganglia. The authors' interest stemmed from a desire to gain a better understanding of the electrical

relations existing between the mesencephalic gray masses and the cerebral cortex and to test the effect of various therapeutic procedures on the electroencephalogram.

Electroencephalographic abnormalities were discussed, as well as the factors involved in producing the electroencephalogram. Technical difficulties of electroencephalographic recording in cases of paralysis agitans, due to tremor; the problems of pharyngeal, tympanic, and directly implanted striatal leads, and the effect of sleep and ablation experiments on involuntary movements were discussed. The neurophysiologic theories of Parkinsonian tremor were cited, and it was emphasized that the characteristic 4-to-6-per-second tremor might be explained by the beat frequency and refractory period of anterior horn cells.

Trihexyphenidyl (artane®) was found to be clinically useful in paralysis agitans, but electroencephalographic findings were variable and inconsistent. Its effect in this study was primarily peripheral; although "silent periods" in the electroencephalogram after trihexyphenidyl were more frequent, a central effect was inconclusive. In four cases of paralysis agitans, thiopental (pentothal®) spindles were not seen before or after administration of trihexyphenidyl, while they occur in normal states and in other conditions.

DISCUSSION

Dr. Joseph F. Hughes: It has been my opinion that the silent periods, described by Dr. Mallin in his electroencephalograms, indicate that trihexyphenidyl has a central effect on the nervous system. The absence of thiopental spindles before and after administration of trihexyphenidyl might raise the question whether the electroencephalogram can be used diagnostically in the study of cases in which early paralysis agitans is suspected.

Dr. Isadore Rose: Our electroencephalographic results would seem to support the clinical impression that trihexyphenidyl is a valuable drug in the treatment of paralysis agitans.

Cervical Air Myelography: A Review of One Hundred Thirty Cases. Dr. Frederick Murtagh, Dr. W. Edward Chamberlain (by invitation), Dr. Henry T. Wycis, and Dr. Michael Scott.

In a series of 130 cases of disease of the cervical portion of the spinal cord and spinal canal 142 cervical myelographic studies with air were performed.

Three methods of examination were discussed, with a summary of the myelographic findings in the normal condition and in congenital malformations, disk protrusions, space-taking lesions, and degenerative lesions of the spinal canal and cord. The indications, limitations, and pitfalls in diagnosis with air as a contrast medium were likewise discussed.

It was the conclusion of the authors that air as a contrast medium in cervical myelography is a valuable means for diagnostic survey of the spinal canal and cord, and that, with the clinical findings, it may often be satisfactory for localization. Negative contrast myelography, through visualability of the cord, is particularly valuable in the demonstration of degenerative and trophic lesions of the central nervous system.

DISCUSSION

Dr. Axel Olsen, Sayre, Pa.: In my experience it has been extremely difficult to interpret the shadows which are produced by air myelography; consequently, I use this procedure only in very special cases. I have abandoned the procedure entirely in study of the lumbosacral area. It is true that air is an innocuous substance in the spinal canal, but since the interpretation of the shadows is difficult, I have come to believe that this medium may lead one astray. I believe that one gets much better information from using ethyl iodophenylundecylate (pantopaque®).

Dr. Henry Shenkin: Several years ago I studied a series of 100 cases in which air had been used for cervical myelography. The results in this series were significantly less satisfactory than the results reported by the authors. Furthermore, I found that patients were made so uncomfortable by the air that if it is necessary to repeat the study one often has difficulty in persuading the patient to accept a second examination.

Dr. Michael Scott: The important point is that air can at times do things that ethyl iodophenylundecylate cannot. I believe there is a place for each procedure. Advanced atrophy of

the spinal cord seems to be better delineated with air, while ethyl iodophenylundecylate is most helpful in the diagnosis of the encroaching syndromes. Furthermore, since the latter drug is irritating, spinal-fluid protein may subsequently be elevated, thus coloring the clinical picture.

The Medical Witness. Dr. Frederic H. Leavitt.

A collateral function of medical practice is the presence of physicians in court to aid in the solution of problems of law in which a medical issue is involved. When a physician goes into court as a witness he is exchanging his customary role of the questioner for that of the questioned; and instead of being the prosecutor in search of medical knowledge, he becomes the accused in his defense of his medical facts and opinions.

The author set forth a series of simple rules that should govern the medical witness and recited some of the discomforting situations that confront the physician in court. The main purpose of the paper was to acquaint the young medical practitioner with the facts and foibles of medicolegal relations.

DISCUSSION

Dr. Francis E. Weatherby, Havertown, Pa.: "Free will" has never been scientifically demonstrated, but it still has never been disproved. Psychiatrists may go to court and deny free will, stating that behavior is biologically determined. Physicians shall leave the latter attitude outside the courthouse and recognize the concept of free will in their testimony.

Dr. Frederic H. Leavitt: We must remember that the man in court has done damage and has hurt someone, and that it is necessary for the court to protect all members of society.

PHILADELPHIA NEUROLOGICAL SOCIETY; NEW YORK NEUROLOGICAL SOCIETY, AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Harold G. Wolff, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, April 27, 1951

Paroxysmal High-Voltage and Rhythmic Low-Voltage Discharges from Isolated and Partially Isolated Human Cortex. Dr. Francis A. Echlin, New York, and (by invitation) Dr. Vitold Arnett and Dr. John Zoll, New York, with the technical assistance of David Peck.

C. E. Henry (*Electroencephalog. & Clin. Neurophysiol.* **1**:378, 1949; ibid. **2**:232, 1950) was the first to report what he termed "suppression-burst activity" from the human cerebral cortex after it had been undercut by Scoville's technique. He therefore deserves the credit for first observing activity of the type with which this presentation is concerned.

The authors summarized their work as follows:

1. Further evidence is presented that rhythmic electrical activity is an inherent property of the human cerebral cortex.

2. After partial or complete neuronal isolation of a block of human cerebral cortex, with the pial circulation left intact, paroxysmal discharges of high-voltage fast waves (20 to 30 cps) superimposed on slow waves occur, with intervening periods of low-voltage rhythmic activity. These paroxysmal, hypersynchronous discharges are present for at least two hours in the human brain, and may occur for at least nine hours in the monkey, after complete isolation of an area of cortex. This abnormal explosive behavior of the isolated cortex is presumably further evidence of the control normally exerted over it by deeper structures.

3. In a chronically isolated portion of cortex paroxysmal bursts of high-voltage slow waves may occur, with intervening periods of relative suppression of electrical activity.

4. Spontaneous rhythmic high-voltage, 3-cps waves have been recorded from the chronically isolated cortex, uninfluenced by reverberating circuits involving deeper structures.

Eight lantern slides were shown, illustrating the discharges from the neuronally isolated and partially isolated cortex (*a*) with thiopental-sodium anesthesia, (*b*) with local anesthesia, (*c*) with the cortex freshly isolated and after isolation for five weeks, (*d*) after electrical stimulation of the neuronally isolated block, and (*e*) in the monkey, after administration of curare and a local anesthestic and with the animal under thiopental-sodium anesthesia.

DISCUSSION

DR. AARON W. MALLIN, Philadelphia: Admittedly, the contributions of electrophysiology to an understanding of the human electroencephalogram are scattered and fragmentary. Such papers as this by Drs. Echlin, Arnett, and Zoll are essential before one can hope to interpret electroencephalographic findings in terms of neurophysiological mechanisms. I wish to thank the authors for their fine work and the opportunity to discuss their paper.

DR. DANIEL SILVERMAN, Philadelphia: The phenomena described by Dr. Echlin and his associates could be due to a combination of several factors, viz., (1) depression of cortical neurons, such as one would see in any isolated group of neurons; (2) a selective alteration of anesthetic effect; (3) a dysfunction, something like the epileptiform spreading depression of Leao, which may be caused by a pia-arachnoid defect. The last factor can be tested by Dr. Echlin if he will leave dural leads in place over the isolated and the nonisolated cortex and then record after operation.

DR. HARRY GRUNDFEST, New York: The question whether spontaneous activity is present normally in cells, or whether it is a function of their many connections and of distant foci, is still unsettled. I hope the experiments that Dr. Echlin and his co-workers have done, and will continue to do will throw light on this problem. I would like to point out in this respect that large doses of curare, greater than the physiological or clinical doses inducing paralysis of respiratory function, will block synaptic activity in the cortex and will, therefore, abolish not only spontaneous activity but also potentials evoked by stimuli afferent to the cortex.

Studies on Headache: Further Observations on Cranial and Conjunctival Vessels During and Between Attacks of Vascular Headache. DR. M. MARTIN TUNIS and DR. HAROLD G. WOLFF, New York.

Wolff and his co-workers demonstrated an increase in the amplitude of pulsation of cranial arteries during attacks of vascular headache.

A new, and relatively simple, method of studying the behavior of the cranial arteries utilizes the principle of the crystal microphone. A standard pressure cup overlying the vessel is attached to a piezoelectric crystal. The pressure changes which accompany each pulsation are thereby converted into electrical impulses. These are recorded on a portable electrocardiograph and represent, in essence, a "plethysmographic" arterial pulse wave. The simplicity of the method makes possible continuous recording over several hours, comparable intermittent records during several days, and simultaneous records from the two sides and from several parts of the head. The amplitude of the waves is indicative of the degree of distention of the vessel with each cardiac systole, and during headache it is related to the intensity of pain experienced. Progressive increase in amplitude of pulsations of the involved artery during the evolution of spontaneous vascular headache was demonstrated. Further, the mechanism of action of various therapeutic agents appear to be a "constrictive" effect on the involved vessel: Diminishing amplitude of arterial pulsations was noted to accompany diminishing intensity of headache after administration of ergotamine tartrate, corticotropin (adrenocorticotropic hormone), and a placebo of isotonic saline.

Patients subject to vascular headache, in contrast to those who do not have headache, were shown to have remarkably labile pulse waves in the temporal artery during a discussion of stressful life situations. Typical vascular headaches were precipitated during such "stress" interviews.

Photomicrographic studies with the slit lamp gave evidence that the conjunctival arterioles, venules, and capillaries all underwent extensive dilatation during headache. Such change was observed to occur on the homolateral side only in eight cases of unilateral vascular headache.

DISCUSSION

DR. HENRY A. SHENKIN, Philadelphia: We are all grateful to Dr. Wolff and his co-workers for elucidating so ably the basic involvement of the vascular system in headache, and an extension of their observations will, I am sure, lead to much greater information as to the source and origin of this important symptom.

DR. H. G. WOLFF, New York: I should like to comment on the advantage which my associates and I find in using this method to follow a patient from the beginning to the end of a long headache, as was not possible with the more cumbersome method we had been using. The extraordinary lability of the blood vessels in persons with migraine headaches, especially at the time of the attack, has been demonstrated. A variety of circumstances may quickly alter the amplitude of pulsations of the cranial arteries in persons subject to headache, whereas similar circumstances of stress are not accompanied by changes in the amplitude of pulsations in persons who do not have headaches.

Failures in Migraine Therapy. DR. ARNOLD P. FRIEDMAN and DR. THEODORE J. C. VON STORCH, New York.

In an approach to the therapeutic problem posed by patients with migraine headache, a consideration of failures in treatment is important. The observations presented were based upon a study of 800 patients who were treated at the headache clinic of the Montefiore Hospital. All patients had the usual features of the migraine syndrome and were followed for one to four years.

It would appear that the commonest causes of therapeutic failure are incorrect diagnosis; inappropriate, inadequate, or improper administration of medication; inflexibility of therapeutic regimen; failure to recognize the variable etiology of the syndrome; additional factors associated with the attack, and, finally, the vital role of the patient-physician relationship.

It was noted that patients refractory to therapy revealed personality disturbances greater in degree than those who responded to treatment. There was a pronounced deficiency in the mechanism whereby they handled their aggression.

These observations have suggested to us that symptomatic therapy in migraine must be flexible and individual; variable, accessory, and complicating factors must be considered in each case; more intensive psychotherapy is indicated in both refractory and responsive patients.

DISCUSSION

DR. JOSEPH C. YASKIN, Philadelphia: One can little question or add to the discussion on the treatment of migraine by two careful investigators who treated 600 patients with migraine, with failure in only 15%. Their profound insight into the problem is best revealed by their ability to ascribe failure of treatment to one or more of seven factors, a point which should prove of therapeutic value to those few of us who remain clinical neurologists.

Effects of Hypnotic Suggestion on Pain Perception and Galvanic Skin Response. DR. LOUIS J. WEST, DR. KARLEEN C. NEILL, and JAMES D. HARDY, New York.

Pain perception and galvanic skin responses of seven hypnotic subjects were studied, the Hardy-Wolff-Goodell radiant-heat apparatus and the "dol scale" originated by these investigators being employed. The study differed in general from previous publications in the following respects: Subjects were studied in various stages of hypnosis; stimuli of measured intensity, instead of pinches or pinpricks, were administered; changes in pain threshold were measured; quantitative estimates of pain intensity were made by the subjects; alterations of ability to discriminate between pains of differing intensities were noted, and quantitative records of galvanic skin responses were utilized, permitting statistical analysis of data from matched pairs.

The following conclusions were drawn from these data:

1. Hypnotic suggestions of anesthesia may alter pain perception by diminishing the perceived intensity of stimuli, by elevating the pain threshold, and by producing anesthesia.

2. Pain discrimination is often disturbed in the presence of hypesthesia or elevation of pain threshold due to hypnotic suggestion.

3. There is a general correlation between the depth of trance and the degree to which pain perception can be altered.

4. Levels of skin resistance are not affected by the hypnotic state.

5. The galvanic skin response to painful stimuli can be diminished, and sometimes caused to disappear, by hypnotic suggestions of anesthesia.

6. The galvanic skin response may be thus affected even when there is no alteration of perception according to subjective reports.

DISCUSSION

DR. MATTHEW J. MOORE, Philadelphia: Can this work, in any way, be given practical meaning with respect to such types of pain as are encountered in cases of inoperable terminal carcinoma, trigeminal neuralgia, and phantom limb.

DR. LOUIS J. WEST, New York: Hypnotic suggestion has been used in a few such cases. I have never had an opportunity to study it myself, but cases have been reported; I think that success would depend upon the skill of the hypnotist and the susceptibility of the patient.

Papilledema and Poliomyelitis. DR. CLINTON WEIMAN, DR. FLETCHER MCDOWELL, and DR. FRED PLUM, New York.

The author treated 103 patients with acute anterior poliomyelitis in the neurological service of the New York Hospital. Five had changes in the optic fundi resembling papilledema. The complication occurred during the early convalescent stage of the disease and was detected by the patient's complaining of diplopia and blurred vision.

All the patients had moderate to severe paralysis of the four extremities and the trunk. Elevation of the optic disks was first noted 11 to 48 days after the acute onset of the illness and lasted from 13 to 140 days. Three of the five patients required artificial respiration and had arterial hypertension at the time papilledema appeared. The remaining two were normotensive. All patients had elevation of the optic disk, with venous distension and absence of physiological cupping. Two of the three hypertensive patients had small hemorrhages about the disk. Visual acuity was unimpaired in all patients, and visual fields, determined on three patients, were found to be normal. Spinal-fluid studies, possible on only three patients, revealed pressures elevated from 180 to 600 mm. of spinal fluid. One patient was studied by ventriculography and dural-sinus venography while elevation of the disks was present; the ventricular system was normal, and the dural sinuses showed no signs of obstruction. The elevated spinal-fluid pressures did not seem to be related to arterial hypertension, artificial respiration, or obstruction of venous drainage of the head, either by the respirator collar or by dural-sinus thrombosis.

Papilledema is apparently not a rare complication of poliomyelitis, but, if present, it appears to be a benign complication of short duration.

DISCUSSION

DR. EDMUND B. SPAETH, Philadelphia: I question the presence of diplopia in poliomyelitis. I wonder whether papilledema is not commoner in poliomyelitis than is generally thought.

DR. J. C. YASKIN, Philadelphia: I shall be on the lookout for papilledema in poliomyelitis in the future, and I hope I shall see very few cases.

DR. GEORGE D. GAMMON, Philadelphia: It is striking that this complication has been observed in the period of convalescence from poliomyelitis, during which the protein is known to rise.

DR. H. HOUSTON MERRITT, New York: I should like to remark on the cause of the choked disks in these patients. Choking of the disk may develop in any patient in whom there is serious interference with respiration. Cerebrospinal-fluid pressure is directly related to cerebral venous pressure. Hyperventilation drains blood from the head and greatly reduces intracranial pressure. If respirations are slow, venous drainage is impaired, and the cerebrospinal-fluid pressure rises. I have found high pressure in patients who have respiration slowed by barbiturate and other poisonings, and I have seen choked disks in patients with poliomyelitis. I have always attributed this to the respiratory embarrassment.

PHILADELPHIA PSYCHIATRIC SOCIETY

Hugo Mella, President, in the Chair

Regular Meeting, May 18, 1951

Acute Recurrent Schizophrenia. Dr. Harold H. Morris Jr.

In our hospital service for acute psychiatric conditions, a syndrome which we have called acute recurrent schizophrenia comprises almost 10% of the admissions for schizophrenia. This syndrome is characterized by abrupt onset of severe psychotic symptoms in a patient who has had a schizoid personality. The onset is frequently related to a history of recent psychic trauma. The psychosis is marked by restlessness, bizarre speech, symbolic behavior, fleeting hallucinations, and vague paranoid ideas. Seldom is overt hostility expressed. Often the recent traumatic event is symbolically incorporated in the speech and actions of the patient.

Recovery is relatively rapid, the entire psychosis rarely lasting as long as four weeks. Recovery is to the point of the patient's prepsychotic personality. Even in a patient who was observed during nine such attacks there was no tendency toward deterioration. Recovery is accompanied with partial insight; the patient is able to recall spontaneously the events of his psychosis and recognizes that he has been mentally ill.

Typically, the first attack occurs at the end of the second decade of life, and a series of repeated attacks may be expected. Some of the acute schizophrenic reactions observed during the war probably fall under this syndrome. The condition should be distinguished from acute homosexual panic states and manic-depressive psychosis. The treatment of choice is conservative; somatic treatment should be withheld, and a favorable prognosis may be given for the immediate attack. The syndrome has been classified with the schizophrenias because the essential criteria laid down by Bleuler for the diagnosis of schizophrenia are present.

DISCUSSION

Dr. A. P. Noyes, Norristown, Pa.: I am glad that Dr. Morris has singled out this group of schizophrenic reactions. I am not sure whether they should be considered as an entity, because in the case of many mental disorders I have a prejudice against classifying them as definite entities. There are certain types of personality which, under stress, tend to exhibit certain common types of adjustment. Are these adjustments disease entities? To be sure, as Dr. Morris pointed out, this type of reaction differs from typical schizophrenia. The patients described by Dr. Morris have strong egos, and they have the strength of these egos to protect them; it is not necessary for them to develop the commoner type of psychotic pattern as a defense. The ego does not lose hold on them, as it does in persons with diminished protective mechanisms, and they do not lose hold on reality. They do not have to regress to the relatively primitive form of behavior. They have a stronger capacity for reintegration. Schizophrenia is a special type of maladjustment, which these patients do not demonstrate. The definition of schizophrenia sometimes given is "a form of maladaptation with characteristic defects of inner harmony, with consistent disturbance of thought and emotion."

We as psychiatrists are much indebted to Bleuler, who was the first to point the way to what might be called the individualistic entity. Where formerly psychoses were classified on a general basis, we have discovered a psychological train of events due to a specific cause. It is quite logical, then, that there should be this type of reaction in some persons; if they had had fewer personality resources, they probably would have regressed.

I wonder whether Dr. Morris would not have found something by means of the Rorschach test? We think of such disorders not as an entity, but as a symptom complex. I have heard someone speak of schizophrenia as acute psychic decompensation. Might not such a disorder as Dr. Morris has described be a form of subacute psychic decompensation?

Dr. Samuel Zeritsky: By a coincidence, Dr. Noyes discussed last year a paper by Dr. Franz Kallmann. He hinted that he was working on manic-depressive psychosis and that the disease might be inherited as a dominant. Dr. Morris may have done a disservice to the cause of scientific investigation in mentioning the case in which the father had a manic-depressive psychosis and the son schizophrenia. This might prove that manic-depressive psychosis is also a hereditary recessive.

DR. HAROLD H. MORRIS: I should like to thank Dr. Noyes for his thoughtful discussion. It has given me some clearer ideas regarding this syndrome. I also regard it as a subacute psychic decompensation.

The Rorschach test was not used while the patients were in the hospital. They were so active that the tests could not be given during their hospitalization.

One of the chief reasons for my giving this paper is that I disagree with the statement that schizophrenia is a hereditary disease. It is not a disease entity because it includes so many different things.

Use of Multiple Therapists in Treatment of the Psychoses. DR. MALCOLM L. HAYWARD and JAMES EDWARD TAYLOR.

Multiple therapy is a course of intensive psychotherapy in which two or more physicians are simultaneously present at all interviews. Its first, and most valuable, use is in clearing up a therapeutic impasse, such as tends to occur in very sick patients, whose transference will build up to such an intensity that it becomes illusional. Second, it does much to solve the problem arising from the intense ambivalence that is present in schizophrenic patients. Treatment is speeded up by the clarification of emotions in the patient's expression of strong affection for one physician and hostility for another. Third, another factor operating in multiple therapy is the intensity of the emotional experiences that can be built up. Dr. Carl Whitaker and his colleagues have found that when three or more therapists work with a patient, the patient thinks of it almost as a cultural acceptance, as though the whole world were with him; feels safer in his dependence on the strength of the therapists and is less guilty over his aggressive or hostile feelings. Devereux has suggested that since the psychotic patient is already suffering from fragmentation of his personality he is unable to benefit from most of his contacts with people, but in the setting of multiple therapy he finds a group of people all working to help him understand his needs and integrate the conflicting forces in his personality. Contrary to the former belief in psychiatry, which stresses the need for the strictest privacy between patient and physician, our experiences have led us to believe that there is a "safety in numbers" and that the patient can feel more at ease about expressing strong feelings, even of sexual attraction, when more than one physician is present. Third, the group can do more than a single physician to produce a strong and integrative emotional experience.

DISCUSSION

DR. M. M. PEARSON: This fine paper should be provocative of further use of this technique.

Dr. Dreikurs states in his recent article that the principle of the dynamics of multiple therapy is similar to that of group therapy. Moreno, in his "psychodrama," introduces other people on the stage and calls them "auxiliary egos."

I should like to mention an interesting personal experience I had this week. A patient was presented to the staff with paranoid schizophrenia of many years' duration. Many of the staff were embarassed by the fact that he seemed quite different before the group than he had in individual therapy and was less hostile. One physician suggested that with a single therapist a patient with paranoid schizophrenia might have some homosexual feelings that manifested themselves in terms of irritability and hostility, while with several therapists he could feel more self-assured. Psychiatry for a long time has stressed the principle of complete privacy in interviews. "Safety in numbers" is one way of expressing this concept. Dr. Hadden has been working with group therapy for some time, and the patients seem to like the idea of having other physicians sit in at a session of group therapy.

How active are the therapists in using this technique? How much prodding of the patients is there? What are the qualifications of the therapists for this technique?

DR. HERBERT FREED: Drs. Hayward and Taylor are to be congratulated on their work and the clarity with which they expressed it. We have a group of neurotic patients at Temple University Hospital with whom we are using a succession of therapists, one at a time, rather than all together. The transference to one therapist is investigated by the next. There is also the problem of manipulation and acting out of the transference on the part of the physician. How

much does a group of therapists act out and contribute to the transference? It does determine the dynamics of transference very quickly. On the same day a patient may relate his dreams to one therapist, and not to another. The results seem to indicate that this type of therapy is very worth while.

DR. MALCOLM L. HAYWARD: As to the matter of interchange, it varies greatly from one patient to another. In some cases two or three physicians may find themselves doing much of the talking back and forth among themselves, more about the patient than to the patient. In other cases there is the other extreme—the patient will fasten on to one therapist very hard and ignore two or three other therapists, creating a stormy situation, as the other physicians will feel left out or will think that one physician is monopolizing the patient. The multiple, or group, setting makes the dynamics very much clearer, as Dr. Freed says.

The qualifications of the therapists have become an important problem. The physician must be as honest as he can, both to his fellow therapists, to the patient, and to himself. Whitaker and his group have used this technique with patients with every kind of disorder—from neurosis to psychosis. As to the problem of the therapist's acting out a role, by and large, when he is dealing with a psychotic patient, the therapist has his role pretty forcibly thrust upon him.

Results with Carbon-Dioxide Sensitivity Tests in Neurotic Patients. DR. PER-OLOF THERMAN (by invitation), DR. MONTE JOSEPH (by invitation), and DR. KENNETH E. APPEL.

The present investigation was undertaken in order to ascertain a possible correlation between various forms of mental illness, and individual differences in the respiratory response to the inhalation of a 5%-carbon-dioxide mixture. Additional studies were made of the basal metabolic rate and the carbon-dioxide content of alveolar air, as well as the clinical effect of carbon-dioxide treatment (30% carbon dioxide in 70% oxygen). The "sensitivity" to carbon dioxide was determined by continuous recording of the respiratory minute volume under resting conditions before, during, and after four minutes of inhalation of 5% carbon dioxide in 95% oxygen, the mixture replacing ordinary room air. The carbon-dioxide-sensitivity "index" was arrived at on the basis of the following formula:

$$\frac{\text{Resting minute volume} \times \text{average increase/min.}}{\text{Actual oxygen consumption/min.}}$$

Of the 40 patients whose psychiatric condition has been evaluated, 23 had symptoms of a neurosis; the remaining 17 were psychotic. Of the 23 neurotic patients, 16 received carbon-dioxide treatment.

No significant correlation was found between any of the factors of sensitivity "index," resting volume, alveolar carbon dioxide, or basal metabolic rate. Nor was it possible to correlate any specific psychiatric disorder with the sensitivity to carbon dioxide. However, when the results were analyzed on the basis of anxiety, it was found that among the carbon-dioxide-sensitive group ("index" $>$ 50), 80% had overt symptoms of anxiety, whereas only 15% of the less sensitive showed any readily detectable anxiety. Of the patients under carbon-dioxide treatment, about half showed clinical improvement, but no correlation was found between the incidence of improvement and the sensitivity to 5% carbon dioxide, to the carbon-dioxide content of alveolar air, or to any of the other factors studied.

Although the results do not indicate a direct correlation between carbon dioxide and mental illness, it is possible that the increased sensitivity to carbon dioxide found in the presence of anxiety symptoms might be related to factors influencing the blood-alkali reserve. However, the implications of these factors or the factors of psychological significance have not been studied in the present investigation.

DISCUSSION

DR. J. C. LILLY: This paper is interesting to me as a physiologist because in normal subjects ("normal" is defined as an unhospitalized person) I have found that the response to carbon dioxide in gradually increasing quantities in respired air goes up very steeply in the region of a 5% concentration. A person at rest will usually be breathing about 7 liters a minute. Air with a 7.5% carbon-dioxide content can be breathed, but with difficulty, and one gets extreme hyperventilation. The minute volume will be up to about 54 liters a minute. This is a tremendous

increase. If the content is increased to 10%, the minute volume will go up to about 70 liters per minute, or 10 times the amount at rest, and about equal to that during extreme exertion. Some patients will become unconscious after about eight minutes of breathing a 10% mixture. I took the liberty of calculating the average for Dr. Therman's patients. The average for all the patients was 16 liters a minute. This is because those who breathed the maximal amount came within the normal range; that is, 1 standard deviation from normal, or about 32 liters a minute. His patient with the lowest volume, a schizophrenic, breathed about 7.8 liters per minute. That is, breathing a 5% concentration did not raise the resting level. There were no normal subjects.

One finds that there is a tremendous drive to breathe, and if one tries to fight this there is an overwhelming sense of suffocation. Apparently, schizophrenic patients up to four minutes show no such response. I have no idea what the response would have been if they had gone much longer. As to anxiety, I think most people breathing 5% carbon dioxide experience anxiety. The subject has to wear a mask, and that gives rise to anxiety. The outstanding fact is that six of Dr. Therman's schizophrenic patients did fall far outside the normal range. On physiological grounds not much is known about the carbon-dioxide mechanism. In animals the respiratory apparatus is found to be extremely sensitive to carbon dioxide. Several respiratory centers have been found—in the medulla and in the brain. Nothing is known about the inhibitory impulses coming from the higher centers in the brain.

This study also says nothing about the effect of high concentrations on any part of the brain except the respiratory centers. Obviously, in one case it is stimulating, and in higher concentrations it knocks them out. Meduna's theory of carbon-dioxide therapy is not supported by sufficient empirical data on volumes recorded from stimulation of various parts of the brain to justify an attempt at therapeutic treatment with carbon dioxide.

DR. J. S. HUGHES: Does Dr. Therman or Dr. Lilly know what a patient recovered from schizophrenia would do under such stimulation? Would he refuse to respond to the stimulating effect after the illness had subsided?

DR. P. O. THERMAN: In answer to Dr. Hughes's question, we are in the process of recording the minute volume in patients after they have recovered clinically, for we have had a good many patients who were in a state of remission, and they had average values indicating the same thing, that is, when a psychotic patient recovers, his physiological status indicates an increased responsiveness.

When Dr. Lilly points out that the data on our patients fall within normal limits, it is not at all surprising to us or, I believe, to any psychiatrist who is interested in physiological reactions within a group of psychotic patients. They fall within normal limits because we did start out with a group of normal patients.

I agree there are not at present enough physiological data to explain the effect of scattering. Why do normal people react so differently? It is difficult to say. We believe that anxiety is one of the factors which will increase the scattering in many normal, as well as psychotic, subjects.

In conclusion, I should like to say that this does not give a final answer to Dr. Meduna's concept of increased carbon dioxide, and consequent increased pressure, in the tissue. We should like to record from all these patients again and correlate the results with their clinical picture.

Experience with Carbon-Dioxide Therapy in Psychiatric Outpatients. DR. A. L. PETERSON.

In an attempt to find an additional effective treatment which might be used in the setting of an outpatient clinic, carbon-dioxide therapy was considered because of favorable results in patients who had proved refractory to the standard therapies. According to the basic technique of Meduna, 30% carbon dioxide and 70% oxygen was used in the treatment of selected patients with psychoneurosis. It was sought to broaden its applicability and efficacy (1) through variations in technique and (2) by the addition of concomitant therapies. We were also interested in making cost and time comparisons with similar results in psychotherapy in the outpatient

clinic. This report is based on experience with 16 patients given a total of 744 treatments. Each patient had a minimum of 25 treatments. Selection of cases was limited to nonpsychotic reactive tension states.

Anxiety often causes a serious problem as a bar to treatment with carbon dioxide. It may arise from several sources, and in about one case in five, some variation in technique is required which will allay anxiety and allow the patient to remain in treatment. Anxiety may exist as a symptom of a neurosis or may arise after several treatments, after being released from an equivalent symptom. The treatment experience is occasionally a serious threat to the ego and may produce further anxiety. Dream-like, subjective experiences in treatment are occasionally quite frightening. In addition, at the deeper levels of carbon-dioxide anesthesia, there is an increase in motor discharge, from which the patient may awake in panic. In order to keep anxiety from these several sources at a minimum, either a prolonged treatment or a second treatment given shortly after the first one may be effective. Barbiturates have been of value and have made for no change in results when used in conjunction with carbon-dioxide therapy. To allow the patient to hold the face mask himself is often the most reassuring single measure for an over-anxious patient. A concomitant psychotherapeutic program is found of value in shortening the course of treatment, and it is also recommended as a means of insulating the patient against a psychogenic recurrence. Preliminary survey of initial results shows a definite improvement in 56% of patients selected for treatment. Approximately 37% of patients treated have improved markedly or have recovered. In point of total time expended, these two categories would correspond to 5 and 11 psychotherapeutic sessions, respectively. Carbon dioxide would seem to have an effect beyond that of mere suggestion. Results indicate that this physiological agent is an effective treatment measure and that it may yield results where other therapy has failed. It would seem to be less expensive and less time-consuming than psychotherapy in similar cases in a clinic setting. Further evaluation must await a longer period of follow-up observation and comparison with psychotherapeutic statistics.

DISCUSSION

DR. WILLIAM LHAMON: There is a great deal of interest in what Dr. Peterson has been telling us. The principal benefit is the saving of time.

I have a few remarks which I think are of special interest. These sensory perceptions are like those with mescaline and also like those with lysergic acid. As to the anxiety over the loss of ego control, how long does it last?

I had a few questions. What about people with ulcerative colitis, with migraine, etc.? I wonder about the presence of synesthesia; do these phenomena occur in a systematic way? Another thing that interests me is the dreams; under psychotherapy these repetitive dreams disappear. I wonder what the mechanism of this is. I believe there were only a few cases in which Dr. Peterson gave psychotherapy concomitantly.

I believe one way in which to reduce anxiety would be to give smaller doses of carbon dioxide, as one does in electric shock therapy. There is less memory disturbance following electric shock when a subconvulsive dose is given. This is also true of oxygen therapy.

Also of interest is the similarity of the perceptions that patients report under Dr. Meduna's treatment to the feeling patients have when they go under anesthesia—of being dropped into the ocean, of flying high, or of falling.

DR. A. L. PETERSON: First, as to the similarity between the action of lysergic acid and that of carbon dioxide in producing sensory effects. I have had no experience with it, although I have been reading of it. I am aware of the similarity to mescaline. With regard to anxiety as a result of loss of ego, I do not know that one can say this anxiety is from one source or another. One may get hints of it, or a patient may say something which will give one a hint. I think the sensory dream experience is another great contributing factor. Physiological anxiety is represented by forceful hyperpnea. One cannot help feeling anxious, and this is an equivalent anxiety symptom. It can largely be controlled with barbiturates. We have had patients who had "road-to-ruin" anxieties or homosexual anxieties. Such patients will sometimes breakdown and will not be able to go on with the treatment.

We are not prepared to give any analysis of results in patients selected for treatment. We had a psychosomatic patient who had the clinical picture of an upper gastrointestinal disorder; he had a peptic ulcer of the duodenum, and the diagnosis was made by x-rays. His symptoms have disappeared, and the ulcer is no longer evident in the roentgenogram. We had another patient, with ulcerative colitis. His bowel movements are now down to four or five a day, and he feels better and requires fewer blood transfusions. We have not treated any patients with migraine.

Synesthesias were not found in any patients whom I have met as yet. Concomitant psychotherapy was carried on in about one-half our cases, and, although the data are not sufficient for valid conclusions, we feel we could prove that this method yields earlier results, and we can almost sense that there will not be any recurrence.

With regard to the "going-under" sensation in anesthesias, I suppose this is also universal, and it is not unusual with carbon-dioxide anesthesia. We explain to patients who have had previous surgical experience that the sensation will be similar, and then we have a basis for discussing it, and they go through it quite comfortably.

Experimentally Induced Conflicts in Animals: A Laboratory Demonstration. DR. E. ROGER WATSON.

The announcement consisted in a mention of the history and rationale of studies in animal behavior, a brief statement of the experimental procedure (derived from Masserman), a brief statement of the findings, and an invitation to a demonstration of these findings to be held in the laboratory after the meeting.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

RADIOACTIVE ISOTOPES IN LOCALIZATION OF INTRACRANIAL LESIONS. S. N. CHOU, J. B. AUST, W. T. PEYTON, and G. E. MOORE, A. M. A. Arch. Surg. **63**:554-560 (Oct.) 1951.

Since intracranial lesions cause a breakdown in the blood-brain barrier, they show an increased uptake of chemical substances introduced into the blood stream. Thus, radioactive isotopes, or "tagged" compounds, may be used in the localization of intracranial lesions.

Radioactive phosphorus (P^{32}) is taken up in significant amounts by cerebral neoplasms. The beta radiation remitted by radioactive phosphorus penetrates only 7 mm. of brain tissue and is therefore not detectable through the intact skull. For this reason, radioactive phosphorus is not suitable for preoperative localization. It requires a direct probing of the brain with a special cannula containing a Geiger-Müller counter.

Radioactive potassium (K^{42}) has a very high uptake in tumor tissue and a strong emission rate of beta and gamma rays. Unfortunately, use of this substance is impractical because of the short half-life (14.2 hours), its considerable uptake by muscle tissue, and its high price.

Radioactive iodine (I^{131}) has, so far, proved to be the isotope of choice. It can be used either as radioactive diiodofluorescein or as radioactive iodine-tagged human serum albumin. Diiodofluorescein permits accurate preoperative localization. (According to Davis, Martin, and Ashkenazy, correct localizations were made in 95% of 340 cases of intracranial lesions.) Diiodofluorescein is not metabolized; it is secreted by the liver and is a harmless substance.

Iodine-tagged human serum albumin has not yet been given sufficient clinical trial but appears promising. It remains in the blood stream for several days and is excreted mainly by the kidneys. Since radioactive iodine is taken up by the thyroid, the danger of radiation damage to this gland exists but can be reduced by blocking the thyroid by preliminary medication with strong iodine solution U. S. P. The optimal counting ratio for iodine-tagged human serum albumin is reached on the third day after injection.

In addition to an increasing variety of isotopes or "tagged" compounds now available, the recording equipment has been recently improved. Scintillation counters are three times as sensitive as the original Geiger-Müller counters. Furthermore, multiple counters simplify the procedure.

LIST, Grand Rapids, Mich.

AN INVESTIGATION INTO THE PRESENCE OF ANTIBODIES AND HYPERSENSITIVITY IN THE ENCEPHALITIS PRODUCED EXPERIMENTALLY BY THE INJECTION OF HOMOLOGOUS BRAIN SUSPENSIONS. K. R. HILL, Bull. Johns Hopkins Hosp. **84**:302 (April) 1949.

Hill states the objectives of his experiments as follows: (1) to produce encephalitis in guinea pigs and rabbits by the injection of homologous brain suspension and an adjuvant emulsion; (2) to correlate the presence of circulating antibodies with the clinical signs and histological changes of encephalitis; and (3) to effect passage circulating or tissue antibody.

Meningoencephalomyelitis was produced in 27 of 32 guinea pigs given subcutaneous injections of a saline suspension of homologous brain in a water-in-oil emulsion of dead tubercle bacilli. Specific complement-fixing antibrain antibodies were demonstrated in 12 of 23 test guinea pigs. Eight animals showing lesions had no demonstrable antibody. The present studies have failed to demonstrate a relation between the meningoencephalitis and the presence of antibrain antibodies. Attempts at passive transfer, using sera or living cells, gave essentially negative results, as did skin tests for hypersensitivity. Attempts to produce encephalitis in rabbits, with methods similar to those described, were in the main unsuccessful, although unexplained lesions were observed in two test animals and in one control animal.

Specific complement-fixing and flocculating antibrain antibodies were produced in rabbits as a result of the injection of saline suspension of brain plus an adjuvant emulsion.

GUTTMAN, Wilkes-Barre, Pa.

COMPARATIVE STUDY OF THE RATE OF ATROPHY OF SKELETAL MUSCLE FOLLOWING ANTERIOR RAMISECTION AND ACUTE ANTERIOR POLIOMYELITIS IN THE RHESUS MONKEY. R. E. M. BOWDEN, Bull. Johns Hopkins Hosp. **89**:153 (Sept.) 1951.

The rates of atrophy of the sartorius, gastrocnemius, and tibialis anterior muscles were studied in 11 monkeys after anterior ramisection. The rates for all three muscles appear to be similar.

The rate of atrophy of the sartorius muscle was studied in 40 monkeys with anterior poliomyelitis. Seventy muscles were available for study, and in all animals they were completely paralyzed, as judged by clinical tests and sometimes by stimulation of the motor nerve. The calculations were based upon an estimation of the weight of the muscle in the normal animal at the time of inoculation of the virus.

Bowden found that the degree and rate of atrophy of the sartorius muscle after poliomyelitis do not appear to differ significantly from those found after anterior ramisection.

ALPERS, Philadelphia.

ANTERIOR CINGULATE GYRUS AND CORPUS CALLOSUM. J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **16**:235 (June) 1951.

From interest aroused by his study of a patient whose only lesion was bilateral destruction of the anterior cingulate gyrus and damage to the corpus callosum, Nielsen examined gross sections of the frontal region of normal brains and reviewed the available reported cases of lesions of the corpus callosum involving the anterior portion.

In a summary of his observations, he points out that irritative and partly destructive lesions (not section) of the anterior portion of the corpus callosum cause a state of emotional excitability, confusion, motor unrest, irritability, and, often, convulsions. As destruction of the corpus callosum progresses laterally, the anterior cingulate gyri are undermined, and their projection systems are destroyed. Undermining of the anterior cingulate gyri in the human subject, when the corpus callosum has been softened, causes complete apathy, with akinesia and mutism.

In all probability, the anterior cingulate gyrus has the same function in the human subject as in the monkey; it is, among other things, the cortical area for emotional expression. Since all action is emotionally motivated, absence of emotional expression leads to absence of all activity. When the corpus callosum is, in addition, degenerated but not severed, the patient has the mechanism of movement interfered with; he has apraxia.

ALPERS, Philadelphia.

STUDIES ON CHOLINESTERASE: VII. THE ACTIVE SURFACE OF ACETYLCHOLINE ESTERASE DERIVED FROM EFFECTS OF pH ON INHIBITORS. I. B. WILSON and F. BERGMANN, J. Biol. Chem. **185**:479, 1950.

In previous investigations the kinetics of the inhibition of cholinesterase was studied with two reversible inhibitors, neostigmine and physostigmine, and two irreversible inhibitors, diisopropyl fluorophosphate and tetraethylpyrophosphate. One common feature was noted in the data obtained, namely, that all four inhibitors appear to act upon the same groups in cholinesterase at which acetylcholine is hydrolyzed. The inhibition of cholinesterase by various inhibitors was investigated as a function of the pH and as related to the electric charge of the inhibitor. These observations have revealed several features of the active surface of the enzyme. Neostigmine cation inhibition is not affected by the pH in the range tested (6 to 10). Physostigmine inhibits strongly at pH 6. The inhibition decreases with increase in the pH. Physostigmine cation is a stronger inhibitor than the base. However, at pH 10 the entire inhibition must be ascribed to the base, since the proportion of cationic form present at this pH was found to be negligible. The rate of hydrolysis of dimethylaminoethylacetate by cholinesterase was tested at pH 6 to 10 and compared with the pH dependence of acetylcholine hydrolysis. The compound was found to exist in cationic and basic forms, depending upon the pH of the medium. The cation was found to be the more active form, but the neutral molecule was also hydrolyzed, though at a much lower rate. Tetraethylpyrophosphate inhibition showed a definite optimum between pH 7 and 8. This was demonstrated in two ways: (*a*) by measuring the inhibition at various pH values and (*b*) by determining at neutral pH the activity remaining after high dilution.

PAGE, Cleveland.

PROCEDURES FOR THE MICROESTIMATION OF NITROGENOUS PHOSPHATIDE CONSTITUENTS. C. LEVINE and E. CHARGAFF, J. Biol. Chem. **192**:465, 1951.

The separation by chromatography on filter paper and the quantitative estimation in minute amounts (5 to 75 γ) of the nitrogenous lipid constituents ethanolamine, serine, and choline are described. The methods were applied to the analysis of several purified lipid preparations and to a survey of the composition of a series of phosphatide fractions from beef brain, in the course of which several novel constituents were encountered.

PAGE, Cleveland.

USE OF ANTIBODY TO INHIBIT A PARTICULAR STEP IN A MULTIENZYME SYSTEM. E. G. KREBS and R. R. WRIGHT, J. Biol. Chem. **192**:555, 1951.

Inhibitory antisera to various enzymes have been studied, but little use has been made of this type of inhibitor as an aid in the study of metabolic pathways. The usefulness of antisera to enzymes in this capacity would depend in part on the specificity of the inhibition. This paper describes a study in which the activity of a multienzyme system was inhibited by the effect of specific antibody on one of the enzyme components. Dextrose fermentation catalyzed by yeast juice was inhibited by antibody to triosephosphate dehydrogenase. Evidence is presented that the site of inhibition is localized at the dehydrogenase step. A limitation to the applicability of antibody inhibition in intact cell systems is shown by the failure of antibody to this glycolytic enzyme to affect fermentation by living yeast cells.

PAGE, Cleveland.

CEREBRAL BLOOD FLOW AND METABOLISM IN PSYCHOSES OF SENILITY. F. A. FREYHAN, R. B. WOODFORD, and S. S. KETY, J. Nerv. & Ment. Dis. **113**:449 (May) 1951.

Without making any clear distinction between senile psychoses and arteriosclerotic degeneration of the brain, the authors investigated the blood flow and cerebral metabolism of patients with these conditions. They found that the patients suffered from decreased cerebral blood flow, increased vascular resistance, and decreased oxygen utilization.

BERLIN, New York.

RETURN OF SENSATION AFTER EXPERIMENTALLY PRODUCED LESIONS IN SCIATIC NERVE OF CAT. I. C. SHERMAN, E. L. TIGAY, A. J. ARIEFF and M. A. SCHILLER, J. Neurophysiol. **12**:1, 1949.

The authors mapped the sensory loss occurring in cats after section of the sciatic nerve or of the various component nerves. They suggest that the region in which light touch sensation is lost immediately after section of a nerve should be considered the area of anatomic sensory supply of that nerve. Along the periphery of this area is a region with preservation of pain. This is the result of dual innervation from adjacent nerves, and this narrow edge, occurring within the periphery of the anatomic sensory supply, should be called the intermediate zone, or the area of dual innervation. The term "residual sensory area" should be applied to that portion of the skin in which sensation is intact when one nerve is intact but the nerves to the adjacent area have been severed.

After nerve section, and without nerve regeneration, the area of anesthesia may shrink, owing to overlap and ingrowth of fibers from adjacent nerves. Loss of touch sense, however, remains constant. The area of isolated supply is that which remains insensitive to all modalities and is permanent. Recovery of sensation here is possible only by regeneration. The authors found that in cats motor function may precede sensory function and that correlation of the two was not possible. The placing reaction occurred before return of cutaneous sensibility. Delay in suture of the sectioned nerve delayed the return of deep pinprick sensation and made doubtful the possibility of recovery of this modality.

FORSTER, Washington, D. C.

MICROELECTRODE STUDIES OF NEURAL AUDITORY ACTIVITY OF CAT: 1. INFERIOR COLLICULUS. W. R. THURLOW, N. B. GROSS, E. H. KEMP, and K. LOWY, J. Neurophysiol. **14**:289 (July) 1951.

Recent conditioning studies with cats have demonstrated the importance of the inferior colliculus in mediating responses to auditory stimuli in this species. From these studies it has been found that the inferior colliculus can function to maintain approximately normal intensity

thresholds and intensity-discrimination thresholds in the absence of the auditory cortex; lacking both the inferior colliculi and the auditory cortex, animals exhibit marked impairment of these thresholds, even after retraining.

The purpose of the present study was to add to the information concerning the neural responses of colliculus structures, the microelectrode technique being utilized.

Neural potentials produced by continuous tones, onset of pure tones, clicks, and thermal noise were recorded from the inferior colliculus of the cat.

Spike responses may appear when recording is performed by means of microelectrodes. These responses show longer latencies, a lower maximum rate of fire, and usually more rapid adaptation and higher thresholds than do similar responses at the level of the cochlear nucleus. However, as at the level of the cochlear nucleus, the spike response is obtained only to a given band of stimulating frequencies, the band width increasing with intensity.

Further evidence for correlation of the position of response effect in the inferior colliculus and frequency of stimulation is obtained from observations on selective frequency masking of click responses. These results reflect the operation of a spatial analyzing mechanism for frequency, evidence for which has been found in other parts of the auditory nervous system.

ALPERS, Philadelphia.

ELECTROPHYSIOLOGICAL STUDIES OF SUBCORTICAL CONNECTIONS OF ANTERIOR TEMPORAL REGION IN CAT. J. STOLL, C. AJMONE-MARSAN, and H. H. JASPER, J. Neurophysiol. **14**:305 (July) 1951.

Subcortical connections with the tip of the temporal lobe in the cat were studied by (*a*) strychnine neuronography, (*b*) electrically evoked responses, and (*c*) electrically induced after-discharges.

Direct two-way connections between the tip of the temporal lobe and the septum via the fornix and to the nucleus lateralis posterior of the thalamus were established by all three methods. Probable direct two-way connections were also established with the basal ganglia (caudate nucleus, pallidum, red nucleus, substantia nigra, and subthalamic region). Corticofugal connections were found only to the hypothalamus (lateral and medial areas). Indirect two-way connections were found between the tip of the temporal lobe and the anterior thalamic nuclei and to the centrum medianum of the thalamus.

Strychnine spikes and sustained electrical after-discharges were recorded from the tip of both temporal lobes after local stimulation of the septal nuclei or of the nucleus lateralis posterior of the thalamus.

Stoll and his co-workers discuss possible relation to physiological effects of stimulating the tip of the temporal lobe and relations of such stimulation to the electroencephalogram and clinical manifestations of epileptic patients with temporal-lobe seizures.

ALPERS, Philadelphia.

THE HUMAN FRONTOCORTICOPONTINE TRACT: FUNCTIONAL INCONSEQUENCE OF ITS SURGICAL INTERRUPTION. R. MEYERS, Neurology **1**:341 (Sept.-Oct.) 1951.

The role of the frontocorticopontine tract in man is as yet obscure. Much of what has been claimed for the human brain up to the present has been reached by inference from animal experimentation rather than from observations on man himself. Some of the claims expressly indicate that damage to the frontocorticopontine tract results in manifest motor disabilities; others do so by implication. Meyers attempts to settle the issue whether any or all of these claims can be supported by data derived directly from human subjects.

The subjects of this study consisted of 23 men and women who exhibited motor disorders commonly termed "extrapyramidal" disease. Twenty-two presented the clinical picture of Parkinsonism of postencephalitic or idiopathic origin. The 23d patient, a woman, suffered from oculogyric crises and severe dystonia of the muscles of the tongue and lower jaw. The disorder in this case was probably of postencephalitic origin.

These 23 patients were subjected to operative procedures in which structures commonly considered to give transit to the frontocorticopontine tract were severed. Of the 23 cases, 15 appeared suitable for final inclusion in this study. Fourteen patients had been subjected, among

other procedures, to surgical section of the anterior limb of the internal capsule for the relief of Parkinsonian tremor. The 15th had undergone section of the medial third of the mesencephalic peduncle for the relief of dystonia of the face, jaw, and tongue.

No neurologic deficits attributable to surgical interruption of the structures mentioned above were demonstrated. Specifically, disorders of muscle tonus; of release, patterning, and energizing of skilled acts; of synergy, and of reciprocal innervation, asserted by various authors to result from damage to the frontocorticopontine tract, did not supervene. For all practical purposes, the operative procedure appeared to be without functional consequence.

Meyers does not consider the negative conclusions arising from this study as final because it cannot be proved that surgical interruption of the anterior capsular limb and the medial segment of the mesencephalic peduncle were accomplished as envisioned until necropsy is performed in at least some of the cases. At present neuroanatomists are not in complete agreement that the frontocorticopontine tract traverses the anterior limb of the internal capsule. Further study should aid in these problems

ALPERS, Philadelphia.

SENSORY DISTURBANCES IN CORTICAL WOUNDS WITH SPECIAL REFERENCE TO PAIN. J. MARSHALL, J. Neurol., Neurosurg. & Psychiat. **14**:187 (Aug.) 1951.

Marshall describes the historical development of the current view with regard to the central representation of pain.

The material for this study consisted of 1,000 cases of penetrating brain wounds studied at a military hospital for head injuries. Among these, 186 cases with permanent sensory loss were found. Eighteen cases are here reported in detail—11 cases of cortical wounds with impairment of pain and temperature sense, 2 cases of cortical wounds with persistent hyperpathia, 2 cases of small cortical wounds with impairment of temperature sense but preservation of pain sensibility, and 2 cases of extensive wounds with loss of discriminative sensation but with preservation of pain sense.

Marshall suggests that the cerebral cortex is concerned with pain sensibility and presents a hypothesis to explain the paradox that while small cortical wounds may affect pain larger wounds do not.

ALPERS, Philadelphia.

Neuropathology

FATALITIES RESULTING FROM EXPOSURE TO SIMULATED HIGH ALTITUDES IN DECOMPRESSION CHAMBERS. W. HAYMAKER and C. DAVISON, J. Neuropath. & Exper. Neurol. **9**:29 (Jan.) 1950.

This paper deals with the clinical and pathologic features of five fatalities in airmen exposed to simulated altitudes of 30,000 to 38,000 ft. (10,000 to 12,666 meters) in decompression chambers.

Although at this level the oxygen partial pressure of arterial blood is decreased, despite the breathing of pure oxygen, it was not hypoxia, but, rather, air embolism, which was regarded as a determining factor in the outcome, the latter leading secondarily to fatal shock. Other factors, such as agglutination of erythrocytes and sludging, could not, however, be ruled out as important in the outcome.

Only two of the men had "bends" and/or "chokes." The disorder was manifested by focal cerebral signs in four men and by apparently uncomplicated, irreversible shock in the fifth.

Most of the pathologic changes in the thoracic and abdominal viscera were those commonly observed in shock. Fat emboli in the lungs in four cases and in the brain in the fifth were believed to have entered the circulation from the bone marrow.

The cerebral changes were characterized by congestive phenomena, ischemic damage of cortical nerve cells, and beginning demyelination and perivascular glial proliferation. Changes in the spinal cord similar to those in caisson disease were observed in one of the two cases in which portions of the spinal cord were studied.

The reason that death occurred in these five men out of the thousands who were subjected to similar tests was not ascertained. The only known factor predisposing to decompression illness which was common to this group was a tendency to adiposity or actual adiposity.

ALPERS, Philadelphia.

CEREBROMENINGEAL GLIOMA WITH LARGE BASILAR EXTENSION. I. BERTRAND and O. CARVALHO, Rev. neurol. **81**:98, 1949.

Bertrand and Carvalho report on a large tumor of the right hippocampus in a man aged 47, who after two months of headache had sudden onset of hemiplegia, hemianesthesia, and homonymous hemianopsia, all involving the right side. He died one month later. Autopsy revealed general enlargement of the entire right hemisphere. The tumor had burst out of the cortex in the hippocampal region and occupied the base of the brain from the right olfactory tract to the peduncle. The structures of the base were pushed to the left. The tumor had then pushed into the orbital lobe in the manner of a meningioma. Histologically, the tumor showed a typical area of glioblastoma multiforme; a large portion of it, however, consisted of a typical astrocytoma, without signs of malignancy. At some distance from the tumor, sections revealed gliosis resembling diffuse astrocytoma, again without signs of malignancy. The tumor had compressed the middle cerebral artery, which was thrombosed, and had thus produced numerous areas of softening in the posterior limb of the internal capsule and the thalamus.

The authors devote considerable attention to the polymorphism of the neoplasm. They state that accurate histological study of a glioma is not possible without samples from many regions of the tumor. The impossibility of making a diagnosis on the basis of biopsy is emphasized.

LEGAULT, Washington, D. C.

CEREBRAL CHANGES IN ECLAMPSIA. V. VORTEL, Schweiz. Arch. Neurol. u. Psychiat. **67**:174, 1951.

Vortel reports two fatal cases of postpartum eclampsia in primiparas. In both cases he noted fibrinoid necrosis in the walls of dilated cerebral arterioles, with escape of fibrin and, in certain areas, of leucocytes. In addition to miliary hemorrhages, hyaline thrombi were seen in the capillaries and leucocytic thrombi in the dilated veins. The process was rather scattered and involved different cerebral vessels in a focal manner, showing a predilection for the cortical arterioles. Granular disintegration of axis cylinders, degeneration of ganglion cells, and circumscribed perivascular edema were observed about the affected vessels. Fibrinoid necrosis in branches of the hepatic artery emphasized the fact that the process was generalized, involving the arterioles of different organs. In a note added when he corrected the proofs of this paper, the author stated that a study of three more cases of eclampsia revealed changes identical with those described in the text.

In considering the pathogenesis, Vortel expresses the view that the process represents a hypersensitive reaction and that eclampsia may belong to the group of mesenchymal diseases which includes essential polyangiitis (periarteritis nodosa), serum sickness, and lupus erythematosus. He also states the belief that the specific arteriolar changes described by him would have been observed oftener in the past had sections been cut from larger blocks of tissue and carefully examined.

DANIELS, Denver.

Meninges and Blood Vessels

MENINGO-ENCEPHALITIS DUE TO BRUCELLOSIS WITH THE REPORT OF A CASE IN WHICH B. ABORTUS WAS RECOVERED FROM THE CEREBROSPINAL FLUID, AND A REVIEW OF THE LITERATURE. E. NICHOLS, Ann. Int. Med. **35**:673 (Sept.) 1951.

The purpose of this paper is to describe another case of meningoencephalitis in which a Brucella organism was recovered from the cerebrospinal fluid and to review the clinical manifestations and laboratory findings associated with this complication of brucellosis through consideration of the available literature.

Nichols reviews certain clinical and laboratory findings in 48 cases of proved or suspected cases of brucellosis of the central nervous system selected from the foreign and the domestic literature. Attention is called to the possibility that this complication may arise at any time during the acute or the chronic phase of brucellosis, and even after a prolonged remission. Brief episodes of hemiparesthesia and paresthesia have been considered a "pathognomonic" feature of the disease, hypothetically explained on the basis of spasms of the Sylvian artery. The

most characteristic feature of the symptomatology of meningoencephalitis due to brucellosis appears to depend not so much on the nature of the symptoms themselves as on the dramatic manner of their episodic occurrence over prolonged periods. Much emphasis has been placed on the extent and predominance of meningeal involvement in the great majority of cases and the frequency of disturbances in cranial-nerve functions, particularly the eighth, presumably secondary to chronic basilar meningitis. Other features of importance are the relative absence of localizing neurologic signs and the presence of a low-grade, variable fever. The spinal-fluid findings are predominant lymphocytosis, extreme variability in the number of cells and the protein content, and the not infrequent occurrence of xanthochromia or other evidence of minor subarachnoid bleeding.

A study of the pathology of brucellosis shows a predilection of the organism for tissues belonging to the reticuloendothelial system and a strong tendency to intracellular parasitism of nonphagocytic cells and to the formation of nodular granulomatous lesions. Necrosis is rare. The various pathologic changes in the central nervous system that have been attributed to brucellosis are reviewed. In general, the extensive and advanced inflammatory reaction in the meninges contrasts sharply with the relatively limited and less intense lesions of the cortical and subcortical tissue.

The diagnosis of brucellosis of the central nervous system, a rare complication of an ill-defined and highly variable infectious disease, depends primarily on its consideration as a possibility in otherwise unexplained cases of meningoencephalomyeloradiculitis, particularly when the illness is prolonged and is accompanied by an intermittent, low-grade fever.

The diagnostic importance of recovering a Brucella organism from the spinal fluid or infected tissue of the central nervous system is apparent, and Nichols stresses the importance in suspected cases of high-speed centrifugation of as large an amount of spinal fluid as can be obtained, for careful culture and guinea-pig inoculation of the sediment. A positive reaction of the blood or spinal fluid in agglutination tests for brucellosis, especially in dilutions of high titer, is of great importance. Skin-sensitivity tests to Brucella antigen and determinations of the opsonocytophagic (hemophagocytic) index are of little help.

The natural course of brucellosis is characterized by a tendency to variable and unpredictable remissions and exacerbations, and apparently to recovery in the great majority of cases. An accurate appraisal of the value of any therapeutic agent is therefore very difficult. Nichols states that the value of combined sulfadiazine and streptomycin has not yet been determined and that their use is not without danger. The results of aureomycin in treatment of acute brucellosis are both encouraging and discouraging.

ALPERS, Philadelphia.

ACUTE SUBDURAL HAEMATOMA. J. W. CHAMBERS, J. Neurosurg. **8**:263 (May) 1951.

For many years it has been stressed that extradural hematoma represents an extreme operative emergency, but little has been said regarding the acute subdural hematoma. Too often the impression has been given that patients with acute subdural hemorrhage always have associated brain damage (contusion, laceration, etc.) of such severity that the situation is hopeless. A certain number of these patients have little or no brain damage other than that secondary to compression by clot and present a picture indistinguishable both in clinical signs and in the rapidity of downhill progression from extradural hemorrhage. With immediate action, and in some cases with a modified operative approach, many of these patients can be salvaged.

This paper points out the not infrequent occurrence of massive bleeding from the inferior cerebral veins and dural sinuses in acute subdural hematoma and stresses a more vigorous attempt to find the actual bleeding points and seal them off. A more posterior operative approach is outlined which permits rapid accessibility to the vessels that in the author's experience have often been involved.

ALPERS, Philadelphia.

NOTES ON COLLATERAL CEREBRAL CIRCULATION AS DEMONSTRATED BY CAROTID ANGIOGRAPHY. A. TORKILDSEN, and K. KOPPANG, J. Neurosurg. **8**:269 (May) 1951.

Torkildsen and Koppang attempt to demonstrate the collateral circulation which is called into activity (1) in cases of obliteration of the internal carotid artery at its beginning near the bifurcation of the common carotid artery, (2) in cases of obliteration at the point where the

internal carotid artery bifurcates into the anterior and the middle cerebral arteries, and (3) in cases of hypoplasia of the internal carotid artery.

Arteriograms show that in cases in which there is partial or complete obstruction of one internal carotid artery not only does blood from the internal carotid artery on the healthy side proceed to the pathologic hemisphere by means of the circle of Willis but blood containing the contrast medium may also descend into the internal carotid artery on the pathologic side for a longer or shorter distance. Such distribution of the medium may take place, for instance, in cases of hypoplasia of the internal carotid artery, in which circumstance it must be presumed that there remains a considerable blood flow through the artery in spite of its diminished diameter.

In cases of bilateral occlusion of the internal carotid arteries, arterial blood may reach the cerebral hemispheres by means of the basilar artery. Possible secondary collaterals, which may develop in cases of long-standing obliteration of the internal carotid artery, are discussed.

The cases presented illustrate different forms of occlusion of the internal carotid artery. Such cases previously have been frequently misinterpreted as cases of cerebral thrombosis. From their angiographic experiences, the authors have learned that in cases of gradual or sudden development of hemiplegia the diagnosis of carotid artery thrombosis should be suspected and angiography, with such possibilities in mind, should not be omitted from the diagnostic procedures.

ALPERS, Philadelphia.

TORULA [CRYPTOCOCCUS] GRANULOMA OF THE CERVICAL SPINAL CORD. A. LEY; R. JACAS, and C. OLIVERAS, J. Neurosurg. **8**:327 (May) 1951.

Infection of the nervous system with Cryptococcus histolyticus usually produces rather widespread meningoencephalitis, with a severe granulomatous reaction in the leptomeninx. Sometimes the lesions may be more limited and localized in the brain, giving rise to minute cysts, with little or no alteration of the leptomeninx. These lesions can simulate a brain tumor.

Cryptococcic granuloma limited to the spinal cord has been recorded only once prior to this report. An extensive granuloma of the cervical portion of the spinal cord in a child 8 years old is reported. The symptoms were those of compression of the spinal cord. The granuloma was removed surgically, and the child, who had severe quadriparesis before the operation, recovered completely. Study of the surgical specimen indicated that the causative organism was C. histolyticus. The authors stress the rarity of the case and advocate surgical extirpation of the granuloma in all similar cases.

ALPERS, Philadelphia.

ARTERIOVENOUS ANEURYSM OF THE BRAIN. R. JAEGER, J. Neurosurg. **8**:335 (May) 1951.

The two cases of arteriovenous aneurysm of the middle cerebral artery reported in this paper illustrate (*a*) the futility of hoping for a cure by ligation of the carotid artery (Case 1) and (*b*) the possibility of producing a cure by ligation of the feeding artery, the middle cerebral (Case 2).

In Case 1 a large arteriovenous lesion of the frontotemporoparietal region appeared to be fed by the middle cerebral vessels in the Sylvian fissure. A craniotomy was performed, but nothing was done to the lesion and the skull was closed. Ten days later the right internal carotid artery was ligated with an aluminum clip. Ten months later the patient was readmitted to the hospital in an unconscious state and died 24 hours after admission. Necropsy revealed that an arteriovenous anastomosis (congenital) in the right cerebral hemisphere was fed by the middle cerebral artery. A large subdural clot from rupture of a cortical vein was the immediate cause of death.

The second case was of interest because the pathologic nature of the aneurysm was almost identical with that of Case 1. The entering middle cerebral artery was clipped, and prompt recovery ensued.

Jaeger stresses the possibility of curing arteriovenous aneurysm of the brain by craniotomy and direct surgical attack.

ALPERS, Philadelphia.

PROGRESSIVE EXTRAPERIORBITAL HEMATOMA. C. F. LIST, J. Neurosurg. **8**:340 (May) 1951.

As any fracture may be associated with subperiosteal hemorrhage, fractures of the orbit may cause extraperiorbital bleeding. As a rule, this predominantly venous hemorrhage remains of minor proportion. In the case reported, however, a slow ooze continued, leading to progressive displacement of the eyeball and compression of the orbital contents. The clinical syndrome was characterized by gradually increasing exophthalmos, chemosis, exposure keratitis, impairment of vision with papillitis, extraocular paralyses, and severe orbitotemporal headaches.

It is advisable in such cases to adopt a conservative course at first, since minor extraperiorbital hemorrhage is self-limited and resorbs spontaneously. If, on the other hand, as in this case, the exophthalmos progresses and endangers the cornea and vision, surgical steps should not be delayed until irreversible damage occurs. The condition in this patient was cured by lateral decompression of the orbit, with removal of the hematoma.

ALPERS, Philadelphia.

EXTRADURAL HEMATOMA OF THE POSTERIOR FOSSA. R. C. SCHNEIDER, E. A. KAHN, and E. C. CROSBY, Neurology **1**:386 (Sept.-Oct.) 1951.

A review of the literature indicates that extradural hematoma of the posterior fossa is rare. When confined to the posterior fossa, the neurologic signs may differ from those observed if the lesion overlies both the occiput and the cerebellum.

Since a definite syndrome cannot be depended upon for establishing the diagnosis, one must frequently rely upon objective signs. A contusion over the occiput with a fracture line in this region, in a case with an increased depth of unconsciousness and no other evidence of a supratentorial lesion, is sufficient to warrant trephination over the posterior fossa. The postoperative prognosis is excellent, provided that the lesion is limited to the posterior fossa.

In the case reported in this article, that of a woman aged 43 who fell in the bathtub, striking her head, there was no skull fracture, but the patient sustained a stellate laceration of the scalp over the external occipital protuberance and was unconscious. After regaining consciousness four hours later, she complained of blurring of vision, dizziness, vague sensations, and difficulty in coordinating her eye movements. Lumbar puncture showed spinal fluid under normal pressure and 400 blood cells per high power field. The Pandy reaction was 1+. Four days later she had two episodes of projectile vomiting and complained of severe headache. She was lethargic, had difficulty in talking and swallowing, complained of numbness in her right hand, and had a tendency to lie on her right side. There was questionable blurring of the nasal margin of the optic disk in both eyes. The tongue deviated slightly to the right. There was definite ataxia in the finger-to-nose test with pronounced dysdiadokinesis on the left side. She stood on a wide base and fell backward even with eyes open. Nystagmus was seen on left lateral gaze. Deep reflexes were hyperactive in the right arm and in both lower extremities. A diagnosis of intracranial hemorrhage of the posterior fossa was made, and a suboccipital craniotomy was performed on the left side, with evacuation of a large extradural hematoma from the left posterior fossa.

On the following morning the patient was alert and no longer dizzy. Ataxia on the left side on the finger-to-nose test began to diminish, so that within 24 hours it had almost disappeared. There was no further difficulty with talking or swallowing. Nystagmus was then present on right lateral gaze, but within two or three days this sign vanished completely. The patient was discharged 11 days after operation, at which time her neurologic status was normal.

In considering the nystagmus in this case, the authors point out that in a previous paper Crosby had evolved the hypothesis that the pyramis of the cerebellum indirectly exerts a regulatory influence on the contralateral vestibular nuclei, with a pronounced effect upon nystagmus. More recently, Cranmer has shown experimentally that this hypothesis is correct for the monkey. The clinical findings in the present case coincide with his experimental work on nystagmus.

ALPERS, Philadelphia.

Diseases of the Brain

CHANGING ATTITUDES TOWARD MULTIPLE SCLEROSIS: A PROGRAM OF MANAGEMENT. E. E. GORDON and K. E. CARLSON, J. A. M. A. **147**:720 (Oct. 20) 1951.

The attitude toward the course of multiple sclerosis is undergoing a change. The "classic" picture has emphasized the rapid progression, the swift onset of helplessness, and the early death. However, a recent statistical study indicates that the median duration of the disease is approximately 27 years, a surprisingly high estimate as compared with previous views.

The chief cause of death in multiple sclerosis is bronchopneumonia. Inactivity appears to be an important underlying factor in the development of bronchopneumonia, decubitus ulcer, and kidney stones. The question arises whether enforced immobilization materially contributes to and hastens death, or whether the course of the disease may be influenced to the extent of prolongation of life by the encouragement and promotion of activity for as long as possible.

In the management of this disease by rehabilitative techniques the broad strategy is directed toward teaching the patient how to manage his life in spite of his handicaps by means of his residual abilities.

The techniques employed to realize these aims are (1) strengthening of residual motor units of a muscle which are only partially removed from voluntary innervation, but which are atrophied from disease; (2) training of synergists for a particular motor pattern in which the neuronal connections to the prime mover are affected; (3) training of other muscles to perform movements to substitute for the normal prime movers irreversibly affected, and (4) use of mechanical devices to compensate for disabilities in order to accomplish purposeful motion required for the numerous activities of daily living.

In addition to procedures of physical therapy, many patients may gain by the pursuit of hobbies. These pursuits afford another method for carrying out integrated motions, with the added advantage of combining purpose with interest.

Bladder disturbances are frequent. In the attempt at rehabilitation, efforts must be directed toward the control of incontinence when it is present. Efforts should be directed toward establishing a reflex bladder, which is the optimal result when the suprasegmental innervation is destroyed. Stress is laid on the need for early urological investigation of all "mild" complaints, with the hope of delaying or preventing sequelae of urinary infection and atonic bladder.

Finally, the physician should promote good hygiene, both physical and mental. Resolution of anxieties may lead to decrease in spasticity. Some patients may need corrective psychotherapy, for it has been found that many patients with multiple sclerosis have basic neurotic traits which warrant attention.

ALPERS, Philadelphia.

CASE REPORT AND SURVEY OF BRAIN TUMORS DURING THE NEONATAL PERIOD. L. ARNSTEIN, E. BOLDREY, and H. C. NAFFZIGER, J. Neurosurg. **8**:315 (May) 1951.

The authors report a case of cavernous angioma of the choroid plexus in a 3-day-old infant. Operation was performed, and death occurred on the second postoperative day.

In a review of the literature of cases of brain tumor occurring during the neonatal period, the tumors were found to be more frequently supratentorial than infratentorial, and about half of those reported appear to have been gliomas. Hydrocephalus appears to have been the only condition common to most of the cases reported in this period, and this was not invariably present. All the cases reported showed a uniformly short course and a poor prognosis.

The presence of tumors during the neonatal period is regarded as supportive evidence for the "embryonal-rest" theory of the genesis of certain intracranial neoplasms. The pathologic nature of the lesions reported lends further support to this thesis.

ALPERS, Philadelphia.

BRAIN TUMOR WITH NORMAL AIR ENCEPHALOGRAPHY AND ARTERIOGRAPHY: REPORT OF AN UNUSUAL CASE. D. W. BLACKWOOD, W. H. MOSBERG, and P. K. ROBINSON, J. Neurosurg. **8**:322 (May) 1951.

This is a report of a case of brain tumor (glioma) that produced hemiparesis, hemihypesthesia, and dysphasia. Carotid arteriography and air encephalography disclosed no abnormality, and at necropsy no displacement of the ventricular system was noted.

The case emphasizes the fact that a glioma may kill its host without producing pathologic changes demonstrable by the ancillary methods of investigation in use today. The most constant diagnostic feature in the natural history of such tumors remains their relentless progressive course.

ALPERS, Philadelphia.

CLINICAL ASPECTS OF CEREBRAL ANOXIA IN MAN. A. T. STEEGMAN, Neurology **1**:261 (July-Aug.) 1951.

The cerebral cortex cannot withstand complete oxygen deprivation for much more than five minutes without undergoing irreversible degenerative changes. The corpus striatum in man is almost equally vulnerable, but the midbrain and medulla are more resistant. The fact that the respiratory and circulatory regulating centers in the medulla can resist anoxia longer permits survival for a variable period after the cortex is damaged irreparably. Variation in the type of symptoms reflects the degree and distribution of cerebral dysfunction, but the actual degree of pathologic damage depends on the severity of anoxia, its duration, and the method by which it is produced.

Steegman reviews the principal courses of anoxia in man and the physiologic effects of oxygen deprivation. He describes the symptoms resulting from complete cerebral anemia, partial cerebral anoxia, and anoxic encephalopathy.

On the basis of the symptoms, he suggests the following classification of anoxic encephalopathy in the residual stage:

I. Primary cortical defects
  1. Diffuse
    (*a*) Emotional instability
    (*b*) Psychotic behavior
    (*c*) Dementia
  2. Focal
    (*a*) Visual defects (central blindness, scotomata, etc.)
    (*b*) Cerebral diplegia
      Symmetrical or asymmetrical, with or without minor sensory changes
    (*c*) Speech defects (dysarthria, aphasia)
    (*d*) Frontal ataxia or tremor
II. Primarily extrapyramidal motor defects
  1. Paleostriatal
    (*a*) Parkinson-like syndrome
    (*b*) Bradykinesia without tremor
  2. Neostriatal
    (*a*) Athetosis
    (*b*) Choreoathetosis
III. Mixed forms
    Variable combinations of I and II.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

SPINAL (LUMBOSACRAL) EPIDERMOID TUMOR, PILONIDAL SINUS, AND PERSISTENT MENINGITIS. E. G. FORGRAVE and K. H. ABBOTT, Bull. Los Angeles Neurol. Soc. **16**:244 (June) 1951.

The congenital defect of the midline structures of the back known as pilonidal cyst, or sinus, is so common that there may be a tendency to lose sight of the not too rarely associated congenital neoplasms of the central nervous system—epidermoid, dermoid, teratoid, and teratomatous tumors.

Forgrave and Abbott describe a case of intraspinal epidermoid (in the cauda equina) associated with a pilonidal sinus in a boy aged 2½ years. Of particular interest in this case was a complicating concurrent purulent leptomeningitis, undoubtedly resulting secondarily from residual organisms in the epidural lumbosacral area, following removal of the pilonidal cyst. After the cerebrospinal fluid became sterile, virulent organisms remained in the epidermoid tumor and in the epidural abscess. So-called plaque disease about the spinal cord above the tumor was demonstrated myelographically and surgically.

That leptomeningitis may occur several months after the removal of pilonidal sinus, as in this case, has not been observed previously. From observation in this case it would seem that infection may lie dormant for months in the spinal epidural fat and/or in the intraspinal tumor following surgical intervention upon the overlying pilonidal defect, only to result subsequently

in infection of the leptomeninges, thus causing a most persistent leptomeningitis. In view of the sterile cultures obtained from the cerebrospinal fluid and the meningeal (purulent) "plaques," it would appear that the failure of the antibiotics to sterilize the tumor and the epidural abscess (positive cultures were obtained from both at the time of operation) may well have been due to the avascular nature of both the tumor and the abscess.

Finally, the authors call attention to the need to recognize the possibility of the occurrence of an intraspinal tumor in children when a pilonidal defect is evident.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

VOCAL CORD PARALYSIS IN HEART DISEASE. M. PLOTZ and M. J. BROOKS, A. M. A. Arch. Otolaryng. **54**:273 (Sept.) 1951.

The association of hoarseness and heart disease is a well-defined, although uncommon, clinical syndrome. The syndrome consists of hoarseness and enlargement of the heart. The hoarseness is the result of paralysis of the left recurrent laryngeal nerve, and laryngoscopy may reveal only the grade of defective movement of the left vocal cord, varying from mere sluggishness to complete paralysis. Involvement of the right side is rare, if seen at all.

The commonest form of heart disease involved is mitral stenosis. Other forms have been described, but in all cases there is enlargement of the heart or one of its chambers. Often, heart failure and dilatation or displacement of the pulmonary vessels are associated.

Plotz and Brooks describe two cases of severe hoarseness and left hemilaryngoplegia in association with mitral stenosis. In one case no improvement was noted on treatment for cardiac disease; in the other there was distinct amelioration of both cardiac and laryngeal symptoms with appropriate treatment directed to the disorder of the heart.

ALPERS, Philadelphia.

ATYPICAL FACIAL NEURALGIA IN THE HYPOTHYROID STATE. F. B. WATTS, Ann. Int. Med. **35**:186 (July) 1951.

A deficiency of the thyroid hormone in the adult may give rise to a syndrome of chronic, recurring pain about the face and neck and recurring headache. The type and intensity of the pain vary considerably and may be manifested as a dull aching or throbbing pain in either carotid area, in or about the ear, in the frontal or temporal area, or along the upper or lower jaw, or in the posterior cervical area. Frequently there may be an associated dull pain or a sense of constriction over the precordium. The pain may be intense or merely a dull ache, but it is annoying because of its chronicity. When a patient complains of this type of facial pain, has recurrent, and at times persistent, headaches, is subject to fatigue and insomnia, and is inclined to be sensitive to cold, the existence of the hypothyroid state is likely. The diagnosis is substantiated by determination of the basal metabolic rate, as well as by exclusion of other diseases by x-ray study of the teeth and sinuses.

Watts presents 29 cases illustrating this syndrome. He found that response to thyroid extract was generally favorable in about two weeks.

ALPERS, Philadelphia.

OPTIC NEURITIS FROM COLD PERMANENT WAVE. J. T. ROBSON and W. CAMERON, Northwest Med. **48**:701 (Oct.) 1949.

Robson and Cameron state that over five years ago a process of utilizing the salt of thioglycolic acid for hair curling was put on the market as "cold wave." Recently reports of toxic reactions to this process have appeared. Attempts have been made to refute these reports by animal and laboratory experiments. It was stated that toxic reactions have an incidence of less than 0.1%. The authors recently treated two patients with optic neuritis in the absence of any cause other than the cold-wave process. The patients were a woman aged 23 and her mother, aged 54. The young woman gave a history of having three home "cold-wave" permanents, the first in July, 1946, and the last in August, 1947, six weeks before the onset of loss of vision in the left eye. The mother gave a history of having used a home "cold-wave" preparation four or five times, the first in March, 1946, and the last in November, 1947. Loss of vision in the

right eye began six months after the first "cold wave," and loss of vision in the left eye began in November, 1947, the same month the last "cold-wave" preparation was used. Mother and daughter were referred to a large midwestern clinic in January, 1948, for further studies, and the possibility of this condition being due to the cold-wave process was stressed. Treatment has been with vitamins and histamine. In the early part of June, 1948, all retinal edema had subsided, but with little return of visual acuity. There is marked pallor of the optic nerve heads, and the appearance is that of a previous optic neuritis. Patch testing was not done because of the danger of reactivating the neuritis. The authors feel that the Pure Food and Drug Administration has been lax in a matter which should be regulated. Mother and daughter have received financial compensation without court procedure.

J. A. M. A.

Cranial Manifestations of Virus Encephalomyelitis (Guillain-Barré Syndrome). P. Michon and G. Alexandre, Semaine hôp. Paris **25**:2939 (Sept. 30) 1949.

According to Michon and Alexandre, there are three types of virus encephalomyelitis (Guillain-Barré syndrome). There may be diffuse meningoencephalic symptoms with manifestations of meningitis and intracranial hypertension in the presence of discrete psychic disturbances. Symptoms of this type may be explained on the basis of congestive and edematous meningitis and bouts of edema of the centers. The second form comprises symptoms of paralysis of the cranial nerves, which may be correlated with the polyradiculoneurotic syndrome. Occasionally these symptoms may be predominant while associated with vague peripheral symptoms, or there may be no symptoms other than those of paralysis. Cerebral paralytic symptoms are manifestations of neuritis of an inflammatory character, but they are essentially regressive because of the periaxial localization of the inflammatory lesions. The third form of the cranial symptoms is characterized by acrodynia, which may be associated with encephalitic and cardiovascular symptoms. These symptoms may be linked with disturbances of the neurovegetative centers. Cerebral symptoms, with their atypical manifestations, may make diagnosis difficult. Examination of the cerebrospinal fluid for determination of the humoral syndrome is of utmost importance in cases in which the symptoms apparently have little in common with polyradiculoneuritis. Meningitic symptoms may first be associated with hypercytosis, while albuminocytologic dissociation may be demonstrated only on repeated lumbar puncture, from the 7th to the 45th day. Death may result in cases of involvement of the 10th nerve and of vegetative functions. The use of the iron lung may be an aid in passing the danger point, and the transitory character of the paralysis may be demonstrated by the resulting recovery.

J. A. M. A.

Treatment, Neurosurgery

Phenacemide in Treatment of Epilepsy. M. W. Tyler, and E. Q. King, J. A. M. A. **147**:17 (Sept. 1) 1951.

The purpose of this paper is to classify and tabulate the extensive clinical reports on the use of phenacemide (phenurone®) in the treatment of epileptic seizures, in order to attain a clearer picture of the uses and limitations of the drug.

In a series of 1,539 patients, approximately 65% showed improvement when phenacemide was given alone or in combination with other anticonvulsants, such as phenobarbital, diphenylhydantoin (dilantin®), and "mesantoin" (methylphenylethyl hydantoin). In 539, or 35% of the total, the seizures were completely controlled or reduced 75% or more in frequency. In 35% of the cases phenacemide therapy was recorded as a failure, either because the treatment did not bring about improvement in the patient's condition or because it became necessary to discontinue the drug when side-effects occurred.

The side-effects most frequently seen were favorable or unfavorable personality changes. Personality changes occurred in approximately 17% of all cases and usually appeared within the first four to six weeks of the therapy. The more serious side-effects encountered were evidence of hepatic damage and changes produced on the hemopoietic system. In addition, in the order of decreasing frequency, gastrointestinal symptoms, rash, drowsiness, headache, and insomnia were produced. Four deaths due to hepatitis and two deaths due to aplastic anemia were reported prior to the initiation of controls for observing the patients.

The dose of phenacemide must be individualized on the basis of the response of the patient. It has been observed by some investigators that side-effects are less likely to develop if the dose is gradually built up to that which will control the seizures. It is recommended that if some degree of control of seizures has been obtained with other medication, such medication be continued and phenacemide added at a dosage of 0.5 gm. three times a day. The dose of phenacemide should be gradually increased above this initial one until seizures are controlled or limiting side-effects develop. An average dose of 2 to 3 gm. a day has been adequate for most adults.

Tyler and King found that phenacemide (phenurone®) has proved to be effective in controlling or definitely reducing the frequency of seizures in a fairly large percentage of patients who have not responded to other anticonvulsant drugs. The patient or his family should be fully aware of the nature of the drug and of the side-effects which may be produced. They should realize there is a certain risk, which must be weighed against the possible benefits derived from its use. The physician should instruct the patient to watch for signs of toxicity and report them promptly. Only enough phenacemide to last for a short, designated interval should be prescribed.

ALPERS, Philadelphia.

SURGICAL TREATMENT OF POSTHERPETIC NEURALGIA BY SUBDERMAL DENERVATION. K. H. ABBOTT and B. C. MARTIN, Neurology **1**:275 (July-Aug.) 1951.

This preliminary report presents the results of surgical treatment of three patients with postherpetic neuralgia involving the spinal nerves. The patients were treated by elevation of skin flaps, based caudally down to the muscle fascia over the entire herpetic scarred area. Each patient had had numerous types of medical and injection treatment and had failed to respond to any therapy.

Excellent relief from the burning pain was achieved in two patients and fair to good results in the third. One patient has had some return of postherpetic neuralgia 1½ years later.

It has been stated that in elevating the skin and subcutaneous tissues one is performing not only a deep subcutaneous sensory denervation of the skin, but also a peripheral (subcutaneous) sympathectomy. The author suggests that postherpetic pain may, in part, be mediated through sympathetic (autonomic) fibers.

For the relief of postherpetic neuralgia, Abbott recommends elevation of the involved skin from the underlying muscles, the dissection following the dermatome patterns, as the operation of choice, particularly in debilitated patients. However, if failure is encountered or if the pain returns later, extensive sympathectomy with rhizotomy or intercostal neurectomies is to be considered.

ALPERS, Philadelphia.

USE OF PHENURONE® [PHENACEMIDE] FOR CONVULSIVE DISORDERS OF CHILDREN. H. M. KEITH, Proc. Staff Meet., Mayo Clin. **25**:594 (Oct. 11) 1950.

Thirty-five children were treated with phenacemide (phenurone®) for periods varying from 3 to 20 months. Keith's results show that of the 35 patients observed for three months or more, 8 (23%) are considered well and have not had any known attacks, 15 (43%) have improved, and 12 (34%) have not benefited from treatment with the drug.

These observations confirm the reports of other workers that phenacemide is a useful addition to the therapeutic agents for epilepsy. It may successfully control attacks of some patients whose attacks have not been controlled by other forms of treatment, even though a gross neurologic defect may be present. In common with most drugs, it may produce unfavorable side-reactions, such as dermatitis medicamentosa, unfavorable personality disturbances, and, in rare cases, disturbance of hepatic function.

ALPERS, Philadelphia.

MORTALITY AND MORBIDITY AFTER TRANSURETHRAL RESECTION IN CASES OF PARKINSON'S SYNDROME. J. R. LONGLEY and E. N. COOK, Proc. Staff Meet., Mayo Clin. **26**:264 (July 4) 1951.

This study was motivated by the deaths of two patients who had the Parkinsonian syndrome and had undergone transurethral resections for prostatism. The deaths occurred close enough together to raise the question whether or not some pathologic change peculiar to this syndrome

had increased the risk probability of the patients. A review was made of 93 consecutive cases of transurethral prostatic resections of patients with paralysis agitans (Parkinson's syndrome) over a 10-year period. Only one death occurred in the group, and the mortality of this group compares favorably with the mortality of all patients, approximately 12,500, who underwent resection during the same period. From this study it would seem safe to say that patients exhibiting Parkinson's syndrome do not present a greater risk for transurethral prostatectomy than the average patient.

ALPERS, Philadelphia.

USE OF CHONDODENDRON TOMENTOSUM EXTRACT, PURIFIED (INTOCOSTRIN®) IN ELECTRIC SHOCK TREATMENT. G. HÖLLWARTH, Wien. klin. Wchnschr. **61**:521 (Aug. 19) 1949.

In the author's experience with 199 electric-shock treatments in which chondodendron tomentosum extract purified (intocostrin®) was given, there was no clinical or x-ray evidence of fracture, while in a control group several cases of fracture of the spine were found.

MASON, New York.

NEW METHOD OF TREATMENT OF CHRONIC ALCOHOLISM. O. SCHILLER and W. SOLMS, Wien. klin. Wchnschr. **61**:536 (Aug. 26) 1949.

Schiller and Solms used tetraethylthiuram disulfide (antabuse®) in treatment of hospitalized patients, giving 1 gm. daily for six days. After the trial of ingestion of alcohol, the patient is discharged from the hospital, but the drug is continued in a dose of 0.5 gm. a day. The patients and their families are requested to keep in touch with the clinic and to report every two weeks. Advanced sclerosis, hypertensive vascular disease, and cerebral damage are considered contraindications to the treatment. The authors emphasize that there is a limit to the pharmacologic treatment of alcoholism, since the drug does not produce a lasting aversion to alcohol; it certainly creates more propitious conditions for psychotherapy.

MASON, New York.

CLINICAL EXPERIENCE WITH CERVICAL BLOCK IN OTOLOGY. H. DWORACEK, Wien. Klin. Wchnschr. **61**:613 (Sept. 23) 1949.

On the assumption that hyperemia may benefit a number of aural conditions, the author treated about 70 patients by means of cervical block. The patient received an average of 10 blocks (5 on each side, given on alternate days) on an ambulatory basis. The following conditions were represented: Ménière's syndrome (hydrops of labyrinth), postmastoidectomy states, chronic otitis media, otosclerosis, chronic adhesions, lesions of the internal ear, and ozena. The Ménière syndrome and the chronic otitis media responded favorably, so that further trials of this therapy are contemplated.

MASON, New York.

Muscular System

ASSOCIATION OF GRAVES' DISEASE WITH MYASTHENIA GRAVIS, WITH A REPORT OF FIVE CASES. G. LEVY, W. R. MEADOWS, and R. M. GUNNAR, Ann. Int. Med. **35**:134 (July) 1951.

Since the introduction of neostigmine as a test for myasthenia gravis, 16 cases of myasthenia gravis associated with toxic diffuse goiter (Graves's disease) have been reported. In this paper, Levy and his colleagues present five cases considered to be instances of true myasthenia gravis associated with toxic diffuse goiter. Unequivocal response of the involved muscles to neostigmine and their sensitivity to curare are considered specific in differentiating myasthenia gravis from thyrotoxic myopathy.

A subject of much controversy in the literature has been the response of symptoms thought to be those of myasthenia gravis to the medical or surgical therapy of an associated thyrotoxicosis. In evaluating the effect of the treatment of the thyrotoxicosis upon the myasthenia gravis, the tendency of both diseases to undergo spontaneous remissions and exacerbations must be considered. To be kept in mind also is the deleterious effect of prolonged, untreated thyrotoxicosis upon the economy of the body. The authors were impressed by the fact that in the two fatal cases

in their series the patients had prolonged, uncontrolled thyrotoxicosis, with resultant emaciation and debility. In three of their five cases there were periods of control of hyperthyroidism with no apparent effect upon the myasthenia gravis.

With these considerations in mind, the authors suggest that all patients with the syndrome of myasthenia gravis and thyrotoxicosis be subjected to the most direct and definite control of the thyrotoxicosis. When enough patients are thus treated, the controversy concerning therapy may be better resolved.

ALPERS, Philadelphia.

STUDIES IN DISORDERS OF MUSCLES: IV. CLINICAL MANIFESTATIONS AND INHERITANCE OF CHILDHOOD PROGRESSIVE MUSCULAR DYSTROPHY. F. H. TYLER and F. E. STEPHENS, Ann. Int. Med. **35**:169 (July) 1951.

Tyler and Stephens present a summary of a detailed clinical study of 34 patients with childhood progressive muscular dystrophy.

The clinical findings in this condition become apparent in the first few years of life, and a characteristic and symmetrical pattern of muscular atrophy develops in childhood. The large muscles of the pelvic girdle are the first to be involved in a process which spreads centrifugally in an insidious fashion, to produce extreme muscular disability. Most of the patients are severely disabled in adolescence and die then or in early adult life. None of these patients has had children.

Among 33 kindreds in which 61 cases of the disorder are known to have occurred, the data are consistent with the interpretation that it is inherited as a sex-linked recessive trait, but with a mutation rate of approximately 1.0×10^{-4}. This high mutation rate accounts for the many apparently sporadic cases of childhood progressive muscular dystrophy.

ALPERS, Philadelphia.

PERIODIC PARALYSIS: A REPORT OF THREE CASES. E. M. HAMMES, J. A. M. A. **146**:1401 (Aug. 11) 1951.

Most patients with acute paralysis suffer from one of three conditions: poliomyelitis, hysteria, or the infectious polyneuritis of Guillain-Barré (virus encephalomyelitis). A smaller percentage have postdiphtheritic neuritis, myasthenia gravis, some forms of toxic neuritis, tic paralysis, porphyria, necrotizing myelitis, or the disturbance of potassium metabolism known as periodic paralysis.

Periodic paralysis occurs more commonly in males, the onset occurring as a rule in adolescence. The attack commences, usually without prodromal symptoms, in one or several extremities and extends in an irregular fashion, there being no typical pattern. It is generally held that the paralysis appears during or after sleep. The muscles supplied by the cranial nerves are, as a rule, spared. On examination the significant findings are confined to flaccid paralysis with diminution or loss of deep reflexes in the involved areas. The disease tends to become less severe with age. Pregnancy has a favorable effect in reducing the frequency and severity of attacks. Death (mortality rate about 10%) is the result of paralysis of the respiratory musculature.

Hammes reports two cases of familial, and one of sporadic, periodic paralysis. In the first case, that of a man aged *27*, the disease had been diagnosed as acute poliomyelitis because the patient was first seen during an epidemic of poliomyelitis and an adequate history of previous attacks was not obtainable. In the second case, that of a man aged *25*, a diagnosis of acute poliomyelitis was also made, the patient having, for unknown reasons, denied his previous attacks. Twice previously, during military service, he had been classified as a malingerer. The sporadic case was that of a nurse aged *26*, with no family history of the disturbance. One year previously her condition had been diagnosed as myasthenia gravis.

The primary disturbance which leads in periodic paralysis to a recurring decrease in serum-potassium concentration is unknown. The common factor in the attacks is the decrease in the serum-potassium level. It seems likely that there are numerous precipitating factors in the attack, and these must be evaluated and controlled in the individual patient. It has been implied by some investigators that a serum potassium of 12 mg. per 100 cc. may be the critical

level which produces paralysis. On the five occasions in the three cases reported in which serum potassium was measured, only one attack was associated with a level below 12 mg. per 100 cc., and in one the level was within the normal range of 18 to 22 mg. per 100 cc.

The possibility of a primary loss of body potassium by excretion was examined by Talbott, who found no appreciable rise in potassium excretion before or during attacks. Hammes concludes that at the onset of an attack the supply of potassium of the body is in some manner drawn into extravascular tissues, probably into intracellular fluid.

The treatment of the attack itself consists of the prompt and liberal introduction into the body of potassium salts and, if necessary, the artificial maintenance of respiration until the potassium deficiency has been corrected.

Hammes states that the giving of potassium salts in adequate amounts is harmless and should be done promptly in any case of acute flaccid paralysis of undetermined origin. This should be preceded by the drawing of a sample of blood for serum-potassium determination. These procedures will not interfere with, or delay, any further diagnostic measures. It may well be that the more widespread use of this procedure will reveal periodic paralysis to be far less rare than is generally believed. The management of the patient between attacks must be as individualized as the control of the patient with epilepsy.

ALPERS, Philadelphia.

MYASTHENIA GRAVIS IN A MOTHER AND HER NEWBORN SON. G. E. MCKEEVER, J. A. M. A. **147**:320 (Sept. 22) 1951.

McKeever describes the seventh known case of myasthenia gravis occurring in a newborn child of a myasthenic mother.

The outstanding features of the case of myasthenia gravis in the mother were as follows: (1) The unusual nature of the patient's initial symptoms had allowed the disease to go undetected for 16 months; (2) the patient experienced a remission during the first five months of pregnancy; (3) a relapse occurred during the sixth month of pregnancy; (4) a remission occurred on the day of delivery; (5) a relapse followed the delivery and, in turn, was followed by a remission; (6) the baby was delivered by Caesarean section, for reasons not related to the myasthenia gravis.

The outstanding features of the case of myasthenia gravis in the baby were as follows: (1) The baby was normal at birth; (2) the symptoms of myasthenia developed gradually from birth, so that they were clearly recognized by the second day of life; (3) the diagnosis was easily proved by oral administration of neostigmine bromide; (4) the baby required no neostigmine after 15 days of life.

McKeever points out that the transient nature of myasthenia in newborn infants should not cause the clinician to consider the problem lightly. Two deaths have been reported in this series of seven cases.

The mechanism of the transient myasthenia in the baby here described and in others is a matter of conjecture. It is certainly related to the mother's illness. It may be postulated that there exists an increase in cholinesterase in the infant. This may be a reflection of increased circulating cholinesterase in the mother. It is also possible that an increase in circulating cholinesterase developed in the baby in response to the neostigmine medication administered to the mother. The latter possibility is more likely, since the baby was well at birth and the symptoms of myasthenia developed in progressive severity several hours after birth. If the increased cholinesterase of the baby were only a reflection of the increased cholinesterase of the mother, it would be expected that the myasthenia would be severest at birth and show progressive improvement. No case of myasthenia gravis in infancy had been observed prior to the introduction of neostigmine (prostigmin®) in 1935.

ALPERS, Philadelphia.

PRIMARY INTRAPULMONARY NEOPLASM (THYMOMA?) ASSOCIATED WITH MYASTHENIA GRAVIS. R. P. MCBURNEY, O. T. CLAGETT, and J. R. MCDONALD, Proc. Staff Meet., Mayo Clin. **26**:345 (Sept. 12) 1951.

A tumor grossly and histologically identical with thymoma encountered in the mediastinum was found in the parenchyma of the middle lobe of the right lung and was successfully removed surgically from a woman aged 65 with myasthenia gravis. The patient apparently received no

benefit from surgical treatment as far as her myasthenia gravis was concerned. Apparently about 15% of patients with myasthenia gravis have an associated tumor of the thymus. From their experience with thymectomy for myasthenia gravis, the authors conclude that the results are highly variable, and there is some doubt whether it is the removal of the thymic tumor or hyperplastic tissue that causes remission in cases in which the condition is benefited.

A review of the literature revealed two other verified cases of ectopic thymoma. Four other cases were noted in which the thymoma was still in the anterior mediastinum, but it was located at a level lower than the usual site of thymic tissue. The location of the tumor in the lung in the case here presented is difficult to explain either on an embryologic basis or on the basis of neoplastic change in cells found normally in the lung. These workers suggest that when one considers a case of myasthenia gravis in which no thymic abnormality is noted in the upper anterior mediastinum, the possibility of ectopia should be kept in mind.

ALPERS, Philadelphia.

Diagnostic Methods

ELECTROENCEPHALOGRAPHIC STUDIES IN THIRTY-THREE CASES OF SURGICALLY VERIFIED INTRACANIAL TUMOR. P. W. LONGO, P. PINTO PUPO, O. PAZZANESE, A. MATTOS PIMENTA, Arq. neuro-psiquiat. **8**:43 (March) 1950.

In 25 of 26 cases of tumors in the cerebral hemisphere the electroencephalogram showed lateralizing signs. In one case of glioblastoma multiforme and in two cases of tumor at the base of the brain the electroencephalogram was normal. In one case of cerebellar abscess there were clinical signs of involvement of the occipital lobe, but no significantly abnormal electrocortical activity. In one case of acoustic neuroma there was bilateral theta activity, especially on the right side. Similar theta activity also appeared bilaterally in two cases of tumors in the diencephalic region. Increased intracranial pressure produced changes in the electroencephalogram in 11 of 13 cases, with no effect on focal electrocortical activity. Gliomas usually caused more diffuse changes in the electroencephalogram; vascular tumors and meningiomas, more focal changes. In 23 cases of this series the record showed delta waves; in 19, phase reversal, and in 12, depression of the alpha rhythm. In two cases the only evidence of focal involvement was depression of alpha rhythm on one side. In other cases such depression was usually found with delta waves. The apparatus used was a six-channel Grass instrument; 12 electrodes were used on the surface of the skull and 2 in the region of the ears.

SAVITSKY, New York.

Congenital Anomalies

INFLUENCE OF MATERNAL AND OBSTETRICAL FACTORS ON FETAL SURVIVAL. J. L. FITZGERALD, G. N. FERRIS, and C. E. TOSHACH, Am. J. M. Sc. **222**:40 (July) 1951.

This study concerns 52 premature and 82 mature infants who failed to survive in a series of 3,751 deliveries. Of this group, congenital anomalies incompatible with life were the designated cause of death in 24.6%. The corrected fetal mortality, excluding malformations, was 1.8% of all mature infants. For the premature infants of all three groups the corrected mortality was 15.3%.

Of premature infants, 43% have obstetrical or maternal complications which adversely influence their chance to survive. These factors were present in 74.5% of mature infants.

The authors believe that breech delivery presents the greatest hazard to both mature and premature infants. Better psychological preparation of the mother for the onset of labor will decrease the need for sedation, to the benefit of the child. Irrespective of the birth weight of the premature infant, a child born without the handicap of obstetrical complication or a sick mother has an excellent chance to survive.

ALPERS, Philadelphia.

BENIGN ESSENTIAL (HEREDOFAMILIAL) TREMOR. C. H. DAVIS and E. C. KUNKLE, A. M. A. Arch. Int. Med. **87**:808 (June) 1951.

Since little attention has been given this relatively common disorder, the present report was submitted as a survey of 14 cases encountered in the outpatient or inpatient service of a general hospital during a 10-year period. The genetic history of the disorder was explored, and a limited appraisal of the value of drug and other therapy was made.

The disease is relatively benign and heredofamilial. The tremor is more or less rhythmical, either fine or coarse, with a rate of 4 to 12 per second. It is occasionally present at rest and inhibited by action, but it is generally decreased or absent at rest and present on voluntary increase in muscle tonus, as when the limb is held in a definite position (static tremor) and is in active movement (kinetic, or intention tremor). It may be accentuated on approaching a goal in point-to-point movement (terminal tremor). The tremor is aggravated by emotional tension, fatigue, or the discomfort of cold. It may be increased by the use of coffee, tea, tobacco, or alcohol in excess. It is relieved by repose, sedation, or sleep. Involvement is principally of the hands, forearms, neck, head, and face, although the tongue, larynx, diaphragm, lower extremities, or, rarely, the trunk may be included. Except for the increased terminal intention tremor, which may interfere with self-feeding and writing, accuracy and coordination are little involved. The characteristic negative features are the lack of increased tone and resistance to passive strength of Parkinsonism (rigidity, postural flexion, masked facies) and the presence of normal, rapid, rhythmical, alternating movements and automatic associated movements. There are no defects in reflex responses or in sensation.

Representative genetic studies demonstrate considerable variety in the patterns of inheritance. Davis and Kunkle confirm the characteristic resistance of the tremor to medicinal therapy. The proper management is explanation and reassurance. The patient must learn to live with his disability, supported by the knowledge that he will not be incapacitated. Recognition of this syndrome is important, for the tremor can be, and often is, confused with that of far less benign syndromes, such as Parkinsonism.

ALPERS, Philadelphia.

News and Comment

FIRST INTERNATIONAL CONGRESS OF NEUROPATHOLOGY

The First International Congress of Neuropathology will be held in Rome, Sept. 8 to 13, 1952.

The first day will be given to the histopathology of demyelinating diseases, with papers by J. Hallervorden (Germany), J. G. Greenfield (United Kingdom), A. Wolf (United States), and I. Bertrand and L. van Bogaert (France and Belgium).

The second day will be given to the histopathology of cerebral vascular disease, with papers by J. H. Globus (United States), W. Scholz (Germany), R. D. Adams and J. J. Michelson (United States), A. Businco (Italy), and K. T. Neuberger (United States).

The third day will be given to the histopathology of schizophrenia, with papers by L. J. Lhermitte, L. Marchand, and P. Guirand (France); L. van der Horst and W. L. Breutsch (Netherlands and United States); V. M. Buscaino and D. Bolsi (Italy), and A. Meyer (United Kingdom).

The fourth day will be devoted to the histopathology of mental deficiencies, with papers by C. E. Benda (United States), G. A. Jervis (United States), M. Minkowski (Switzerland), W. E. Maffei (Brazil), and K. Inglis (Australia and New Zealand).

The fifth day will be given to the histopathology of senility, with papers by F. Bonfiglio (Italy), P. Divry and F. Morel (Belgium and Switzerland), H. Spatz (Germany), a speaker from Argentina not yet assigned, and G. R. Lafora (Spain).

On the sixth day there will be a free forum for individual presentations. Four sections are being organized for this purpose, the first dealing with the histopathology of demyelinating diseases, the second with the histopathology of vascular diseases, the third with the pathology of schizophrenia, mental deficiency and senility, and the fourth being given to the demonstration of new histologic techniques.

DR. HANS H. REESE ELECTED CHAIRMAN OF MEDICAL ADVISORY BOARD OF NATIONAL MULTIPLE SCLEROSIS SOCIETY

Dr. Hans H. Reese, president-elect of the American Neurological Association, has been appointed chairman of the Medical Advisory Board of the National Multiple Sclerosis Society for a two-year term. Dr. Reese is professor of neurology and psychiatry of the University of Wisconsin Medical School and chief of its department of neuropsychiatry.

The newly appointed vice-chairman of the Society's Medical Advisory Board is Dr. Richard M. Brickner, assistant clinical professor of neurology, Columbia University College of Physicians and Surgeons, New York. Dr. Brickner is also associated with Mount Sinai Hospital, New York.

Dr. Tracy J. Putnam, formerly chairman of the Medical Advisory Board, has been appointed honorary chairman of the board.

ANNUAL MEETING OF AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

The Sixth Annual Meeting of the American Electroencephalographic Society was held at The Hotel Claridge, Atlantic City, N. J., on Saturday, May 10, and Sunday, May 11, 1952. The scientific meetings were held on Saturday afternoon and in the evening, after a subscription dinner, which took place at 7 p. m. Members, their wives, and guests could attend the dinner. On Sunday morning from 10 a. m. to 1 p. m. a symposium on "Electroencephalogram in Relation to Psychiatry" was held. Dr. Denis Hill, of the Maudsley Hospital, London, England, participated in the symposium as a guest of the society. Dr. Hudson Hoagland was chairman of the symposium.

FELLOWSHIP IN CHILD PSYCHIATRY

Fellowships offering specialized training in child psychiatry are available in a number of member clinics of the American Association of Psychiatric Clinics for Children which have been approved as training centers by the Association. The training begins at a third-year postgraduate level, with minimum prerequisites of graduation from medical school, a general or rotating internship, and a two-year residency in psychiatry—all approved. The majority of these clinics have also been approved individually by the American Board of Psychiatry and Neurology for a third year of training and for an additional year of experience.

This training is in preparation for specialization in child psychiatry, and especially for positions in community clinics devoted wholly or in part to the outpatient treatment of chilren with psychiatric problems. At the completion of training, attractive openings are available in all parts of the country. Fellows receive instruction in therapeutic techniques with children in outpatient settings which utilize the integrated services of the psychiatric clinic team. Most of the clinics have a two-year training period, although a few will consider giving one-year training in special cases.

Fellowship stipends are usually in line with United States Public Health Service standards, that is, approximately $3,600, as these stipends come mainly from the Public Health Service. Stipends sometimes are paid by state departments of mental health, the individual clinics, and occasionally communities paying for the training of pyschiatrists engaging to work in these communities at the end of their training. Special arrangements may be made occasionally to supplement the stipends by taking on other responsibilities locally, e. g., part-time work with the Veterans Administration and consultation to social agencies. A limited number of training centers can offer higher stipends.

The office of the American Association of Psychiatric Clinics for Children acts as a clearing house for applicants. Application may be made through this office or directly to the individual clinics. In all cases, acceptance of applicants for training is by the individual training centers.

For further information and for application forms, write Miss Mary C. Bentley, Executive Assistant, American Association of Psychiatric Clinics for Children, 1790 Broadway, Room 916, New York 19.

THE AMERICAN NEUROLOGICAL ASSOCIATION

The Seventy-Seventh Annual Meeting of the American Neurological Association was held at the Hotel Claridge, Atlantic City, N. J., from May 8 to 10, 1952.

Books

Lehrbuch der Neurologie: Die Nervenkrankheiten. Georges Schaltenbrand. Price, 46 German marks; cloth, 87 marks. Pp. 880, with 539 illustrations (many in colors). Georg Thieme, Diemershaldenstrasse 47(14a), Stuttgart-O (American Zone), 1951.

This is the second volume of a "Lehrbuch der Neurologie"; the first volume will be concerned with the technique of examination, the basic scientific foundations for interpretation of clinical neurological syndromes, and the description of those syndromes. This is a colossal task for a single author, but such a treatise has been needed since Oppenheim's classic work has become obsolete, and Professor Schaltenbrand is well qualified to accomplish it. He was well trained in fundamentals in the laboratories of Magnus (Utrecht), Brouwer (Amsterdam), and Cobb (Boston). He spent a year in the neurosurgical clinic of Cushing, was many years the assistant of Nonne, and is head of the neurological clinic in Würzburg. With an excellent knowledge of the English and French languages, he has been in a position to follow the literature of neurology in most of its essential sources, but, during the war, the latest developments were not available to him while writing this book.

The present volume is concerned primarily with disease pictures. Of course, such a subdivision of neurology into basic science, symptomatology, pathology, and clinical disease cannot, in the present incomplete state of knowledge, be carried through rigorously. So the discussion, for example, of the extrapyramidal conditions in Chapter XIV is largely and necessarily concerned with syndromes rather than with diseases, and brief discussions of symptomatology are necessary in many other chapters.

The book begins with disturbances of the spinal fluid. A condition of spontaneous aliquorrhea is described in which there is almost no spinal fluid. The condition is found only in women who suffer from severe headaches. This strange malady we have never observed. The description of hydrocephalus follows along classic lines. In the discussion of Ménière's disease nothing is said about treatment by Fuerstenberg's diet. It is advised not to put sulfonamide drugs into the spinal canal, but penicillin is said to be used to no purpose unless it is injected intraspinally for meningitis. This is contrary to our experience. My colleagues and I obtain just as good results by intramuscular injection of penicillin and advise against the intraspinal use of any medication whatever. The use of any of the antibiotics intraspinally is apt to cause trouble. Moreover, the clinician must be prepared, in treating any meningitis, to have annoying complications arise even after the causative organisms have been destroyed.

In Chapter III the concept of brain swelling is discussed in contradistinction to edema. We admit that we have never observed this condition and do not understand what is meant by it; we doubt whether there is any profit to be made out of it. In Chapter IV metastatic tumors are said to constitute about 6% of all brain tumors. We believe that this is an underestimate (Bailey, P.: Hirngeschwülste, Ferdinand Enke, Stuttgart, 1951). In general hospitals they are as frequent as 16%. In Chapter V one misses the sinuses described by Walker and Bucy. In Chapter VI the recently advised hemispherectomies are not discussed; perhaps it is best to pass over the matter in silence. In Chapter VII the author's remarks about the hypophysial-hypothalamic relations are very judicious, but he still talks of a basophilic syndrome; we feel that there is no justification for relating Cushing's syndrome primarily to the basophilic cells of the hypophysis. It might perhaps be wise to insist that hypophysial hormones are not available in sufficiently pure form to be clinically useful; the commercial preparations are ineffective. In Chapter VIII one misses a discussion of corticotropin (ACTH) and cortisone; however, this is not a treatise on endocrinology. The most frequent tumor in the epidural space (Chap. XIII) is Hodgkin's; we have never found a chloroma. In Chapter XVII one misses the electroencephalographic tracings to be found in all our treatises. In Chapter XVIII the author uses Babinski's definition of hysteria. His remarks about the functional disturbances are reasonable but are apt to satisfy none of the warring sects. In Chapter XIX nothing is said of the practice popular in this country of

injecting the stellate ganglion early after cerebral thrombosis. In Chapter XX the use of dimenhydrinate (dramamine®) in the treatment of seasickness is not mentioned. In Chapter XXVI the author discusses fully the various theories of causation of multiple sclerosis and states his belief, based on personal research, that the disease is caused by a virus related to one which gives rise to a demyelinating disease in monkeys.

There are a few typographical errors and, in Figure 499, the photographs are exchanged. But all these things are minor defects. There is only one serious error which we found, namely, in the pathological anatomy of Japanese B encephalitis. The lesions in that disease resemble so closely those of acute anterior poliomyelitis that they cannot be distinguished by microscopic examination alone.

The book ends with an extensive bibliography, which covers 72 pages.

It is difficult to praise this book too highly. The language is clear and concise; the style is interesting, and the iconography is excellent and abundant. The type is large enough to read easily. The information conveyed is, with very few minor exceptions, accurate and up-to-date. The book is a welcome addition to any neurological library.

Tratamento cirúrgico das moléstias mentais (leucotomia). By Mario Yahn, A. Mattos Pimenta, and Afonso Sette Junior. Prologue by Egas Moniz. Price not stated. Pp. 293, with illustrations. Gráfica e editóra Edigraf, Ltda., Rua da Figueira, 701/5; Caixa Postal 234-A, São Paulo, Brazil, 1951.

Seven of the ten chapters in this monograph on psychosurgery have already been published by the authors in medical periodicals, but the volume brings these together in satisfactory fashion and welds them into a relatively complete whole. Leucotomy has been the subject of study in Brazil for nearly fifteen years, and statistics on its effectiveness are available for more than 400 cases. The authors devote special chapters to the effect of leucotomy in epileptic patients and in children, and they also compare the original Moniz method with the Freeman and Watts technique. A study of the parietal and temporal operations has indicated their inferiority to frontal leucotomy. A three-stage frontal leucotomy, with severing of the basal quadrant on each side, followed by section of the superior quadrants in obdurate cases, has permitted the authors to return an appreciable number of patients to effective living without the damaging effects of excessive disconnection of the frontal lobe.

In undertaking operations on children, the authors concentrated upon patients showing the severest types of conduct disorders, irrespective of the diagnosis. "The operation was particularly effective on symptoms such as exhibitionism, destructive, and perverse trends, impulsiveness, logorrhea, verbal automatism, epileptic seizures, anxiety crises, outbursts of rage, tendency to escape, and environmental apathy." On the other hand, leucotomy in epileptic patients, while followed occasionally by reduction in abnormal behavior, did not exert any striking change in either the fits or the personality. Most of the chapters are supplied with English summaries. On the whole, this volume is useful to those interested in the development of psychosurgery. It reports explorations in various fields with various techniques. The results are conservatively expressed. Leucotomy is considered as an adjuvant treatment, rather than as a definitive treatment, for mental disorders.

HISTORY OF AMERICAN PSYCHOLOGY

by A. A. Roback

Here is the first history of American Psychology ever to appear, showing through development stages how this vastly significant aspect of human study reached its present importance. The volume presents an over-all picture covering three centuries, including the numerous divisions and activities of the powerful American Psychological Association.

Author of more than twenty books on human behavior (many translated into foreign languages), and as one who stood close to the chief architects of the science, Dr. Roback naturally possesses much first-hand information. The ever-growing importance of the subject to students, researchers, psychologists, and intelligent laymen renders this an invaluable tool for study, reference, and genuine interest. Copiously illustrated. $6.00

Expedite Shipment by prepayment

LIBRARY PUBLISHERS

8 West 40th St., New York 18, N. Y.

Out of My Later Years

by

ALBERT EINSTEIN

THIS IS THE FIRST new collection of papers, since 1936, by the eminent physicist. A considerable number of these essays have never been published before in any language.

FROM THE CONTENTS

The Theory of Relativity $E=MC^2$
Time, Space and Gravitation
Physics and Reality
The Fundaments of Theoretical Physics
The Common Language of Science
The Laws of Science and the Laws of Ethics
An Elementary Derivation of the Equivalence of Mass and Energy
Science and Civilization
A Message to Intellectuals
A Reply to Soviet Scientists
Atomic War or Peace
Military Intrusion in Science

Isaac Newton — Johannes Kepler
Marie Curie — Max Planck
Paul Langevin — Walther Nernst
Paul Ehrenfest — $4.75

PHILOSOPHICAL LIBRARY

Publishers

15 E. 40th St., Dept. 370, New York 16, N.Y.

(Expedite shipment by enclosing remittance)

MAKE YOUR office TALK

COMPANION CHAIR

For waiting and consultation. Sturdy comfortable conventional design matches your furniture or Robert James line.

EXECUTIVE DESK

60 x 30-inches. Genuine Walnut. Six drawers with one for files. Top drawer locks all drawers.

Catalogue on Request (Chairs and Desks Only)

EXECUTIVE CHAIR

Seng tempered steel Swivel & Tilt control. Solid Walnut . . . heavy stainproof DURAN cover.

FREE TRIAL
OPEN ACCOUNT
EXPRESS PRE-PAID

ORDER DIRECT

Attach letterhead or mail completed coupon

EXECUTIVE CHAIR brown red green COMPANION CHAIR brown red green EXECUTIVE DESK

NAME: .....

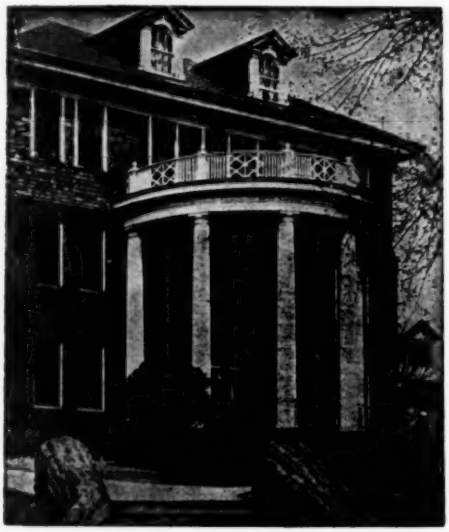
ADDRESS: .....

CITY & STATE: .....

ROBERT JAMES CO.
4107 3rd Ave. S., Birmingham, Ala.

HIGHLAND HOSPITAL, INC.

FOUNDED IN 1904 **ASHEVILLE, NORTH CAROLINA**



AFFILIATED WITH DUKE UNIVERSITY

A non-profit psychiatric institution, offering modern diagnostic and treatment procedures—insulin, electroshock, psychotherapy, occupational and recreational therapy—for nervous and mental disorders.

The Hospital is located in a sixty-acre park, amid the scenic beauties of the Smoky Mountain Range of Western North Carolina, affording exceptional opportunity for physical and nervous rehabilitation.

The OUT-PATIENT CLINIC offers diagnostic services and therapeutic treatment for selected cases desiring non-resident care.

* *

R. CHARMAN CARROLL, M.D.
Diplomate in Psychiatry
Medical Director

ROBT. L. CRAIG, M.D.
Diplomate in Neurology and Psychiatry
Associate Director

BLYTHEWOOD

Founded in 1905 and recently placed under new management, BLYTHEWOOD provides a dignified estate setting for the diagnosis, care and treatment of all types of nervous and mental disorders, including selected cases of alcohol or drug addiction.

Eighteen separate buildings and individual cottages supply complete classification and facilities to meet individual needs.

All recognized types of psychiatric, physical, occupational and recreational therapies are available and utilized as indicated in particular cases.

Access to and from the metropolitan area of New York City by either rail or automobile is quick and convenient.

Stanwich Road, Greenwich, Conn. Greenwich 8-4100

GEORGE W. HENRY, M.D.
Medical Director

Justillien H. Foret, M.D.
Resident Psychiatrist

Gerald R. Jameison, M.D.
Psychiatric Consultant

STAFF

Paul V. Anderson, M.D.
President
Rex Blankinship, M.D.
Medical Director
John R. Saunders, M.D.
Associate
Thomas F. Coates, M.D.
Associate

A private psychiatric sanatorium offering modern diagnostic and treatment procedures — electro-shock, insulin, psychotherapy, occupational and recreational therapy—for nervous and mental disorders and problems of addiction.

Westbrook is located on a 125 acre estate of wooded land and spacious lawns, affording opportunities for outdoor recreational activities. Illustrated booklet on request.

Phone 5-3245 • • Richmond, Virginia

Founded 1879

RING SANATORIUM

Eight Miles from Boston at an Elevation of 400 Feet

For the study, care and treatment of emotional, mental, personality, and habit disorders.
All recognized psychiatric therapies are used as indicated.
Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

BENJAMIN SIMON, M.D.
Director

Arlington Heights, Massachusetts
Telephone AR 5-0081

CHARLES E. WHITE, M.D.
LOUIS BRENNER, M.D.
WILLIAM R. SHELTON, M.D.
Associates

Consultants in all specialties.

FRANCIS W. RUSSELL
Executive Secretary

HARWORTH

531 E. Grand Blvd., Detroit 7, Mich. Walnut 3-7319

Harworth Hospital provides an ideal staff and environment for the care and treatment of

ALCOHOLISM exclusively

Staff: Reg. Int. Med. Spec. • Psychiatrist • Reg. graduate nurses only

North Shore Health Resort

on the shores of Lake Michigan

WINNETKA, ILLINOIS

NERVOUS and MENTAL DISORDERS
ALCOHOLISM and DRUG ADDICTION

Modern Methods of Treatment

MODERATE RATES

Established 1901
Licensed by State of Illinois

Fully Approved by the
American College of Surgeons

SAMUEL LIEBMAN, M.S., M.D.
Medical Director

225 Sheridan Road **Winnetka 6-0211**

PAMPHLETS ABOUT Vision

Whom Shall I Consult About My Eyes? F. T. Jung. 8 pages. 15 cents.

Eyes—Right! Audrey McKeever. 14 pages. 15 cents.

How to Save Your Eyes. Cleo Du Bois. 4 pages. 15 cents.

Should Your Child Wear Glasses? J. Robert Burke. 12 pages. 15 cents.

Color Blindness. Dean Farnsworth and Conrad Berens. 2 pages. 15 cents.

New Eyes for Old (Corneal Transplant). Max Fine. 10 pages. 20 cents.

Glaucoma. Arthur A. Knapp. 12 pages. 15 cents.

Cataract. Abram B. Bruner. 12 pages. 15 cents.

Please remit with order

AMERICAN MEDICAL ASSN.

535 N. Dearborn St. • Chicago 10

"Twenty Minutes from Times Square"

RIVER CREST SANITARIUM

ASTORIA, L. I., NEW YORK CITY

A MODERN SANITARIUM for NERVOUS and MENTAL patients with special facilities for ALCOHOLIC cases. Physicians are invited to cooperate in the treatment of patients recommended.

All Types of Recognized Therapy

REASONABLE RATES

Exceptionally located in a large beautiful private park EASILY ACCESSIBLE BY ALL CITY RAPID TRANSIT LINES.

Six attractive buildings, with complete classification.

Information on Request

LAYMAN R. HARRISON, M.D., Physician in Charge
JOHN CRAMER KINDRED, M.D., Consultant

Long Established and Licensed—On A. M. A. Registered Hospital List

BELLE MEAD SANATORIUM

BELLE MEAD, N. J.

For NERVOUS, MENTAL and ALCOHOLIC patients and ELDERLY people.

FOUR ATTRACTIVE MODERN BUILDINGS with PROPER CLASSIFICATION

Scientific Treatment—Efficient Medical and Nursing Staff
Occupational Therapy

BOOKLET SENT ON REQUEST

Located on 300 ACRE MODEL FARM, at the foot of the WATCHUNG MOUNTAINS—1¼ hours from NEW YORK or PHILADELPHIA, via Reading R. R.

JOHN CRAMER KINDRED, M.D., Consultant

Telephones { Belle Mead 21
New York—AStoria 8-0820

Long Established and Licensed—On A. M. A. Registered Hospital List

FOR CHILDREN

with educational, emotional or speech problems

School problems are directed by the school psychiatrist and an excellent staff of teachers, occupational and recreational therapists, housemothers, and a clinical psychologist. The children are grouped into units, each having its own housemother, teacher and therapists. Every day these staff members note the behavior of each child and review it at the daily staff conference conducted by the school psychiatrist. The psychiatrist discusses the child's family constellation and his pathological relationships and then outlines the program to be followed. These conferences provide a longitudinal study of the child's behavior and enable the psychiatrist to help the teachers and housemothers understand the child. He advises them on attitudes to be maintained toward the youngster and suggests ways of handling specific problems that have arisen in the child's relationship with other children or staff members.

For further information please write the Registrar, 1700 Broadway, Ann Arbor, Michigan.

The Ann Arbor School

Member of the American Hospital Association and licensed by the Department of Public Instruction

ADAMS HOUSE

Established 1877

☆

A non-commitment sanitarium and clinic, club-like in physical setting and atmosphere, applying re-educational psychotherapeutic methods in the study and treatment of the **psychoneuroses** exclusively.

Located in suburban Boston contiguous to and overlooking the Arnold Arboretum

☆

James Martin Woodall, M.D., Medical Director

990 CENTRE STREET, BOSTON,
Jamaica Plain, MASS.

FELLOWSHIPS IN NEUROLOGY AND PSYCHIATRY

Recent developments permit of an expansion of a 3 year fellowship training in neurology and psychiatry at the University of Wisconsin. An accredited and totally integrated training program with the Medical School and all of the Institutions under the Department of Public Welfare is being activated as of July 1, 1952.

There are four (4) vacancies for first year fellowship in psychiatry at $2500 per annum including board and room; one (1) vacancy for a "fellow," who has had a year of residency in psychiatry elsewhere at $3000 plus room and board. There is one (1) vacancy for a first year "fellow" in neurology at $2500 plus maintenance.

Immediate application with submission of credentials is desired. Before selections are made interview may be requested.

For further information write to

DR. WILLIAM J. BLECKWENN
Chairman
Department of Neuropsychiatry
University Hospitals
1300 University Avenue, Madison 6, Wisconsin.

from *Guatemala*

to Green Bay...

worldwide reports (NOW 1842)

worldwide acceptance

.. of one anesthetic

In 1934, when Abbott introduced its new ultra-short-acting barbiturate, intravenous anesthesia was not yet an accepted procedure. Now—18 years and over 1800 clinical reports later—PENTOTHAL Sodium and intravenous anesthesia have emerged as a drug and technique of choice in an ever-increasing number of major and minor surgical operations. • From the start, many anesthesiologists recognized the special merits of PENTOTHAL and intravenous anesthesia. Induction is rapid and pleasant. There is complete surgical amnesia and the patient usually awakens without nausea. The explosion hazard is obviated. PENTOTHAL requires no bulky, frightening equipment. And experience has shown that PENTOTHAL may be used in combination with other anesthetics to meet a specific patient requirement. • Write for more information on PENTOTHAL—investigate its potentialities in a wide range of applications, including obstetrics. Abbott Laboratories, North Chicago, Illinois. Abbott

Send for new book . . .

"PENTOTHAL Sodium by Rectum"

Thirty-six pages discussing the clinical value of PENTOTHAL by rectum for preanesthetic hypnosis and basal anesthesia—results from nearly 4000 cases.

Pentothal® Sodium

(Sterile Thiopental Sodium, Abbott)

FOR INTRAVENOUS ANESTHESIA